IDIOPATHIC APLASTIC ANÆMIA

Incidence and Management

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" IN the classical idiopathic form of aplastic anemia, the course is progressively, inexorably, and more or less rapidly fatal in spite of blood transfusions. Death ensues in the course of a few weeks or life may linger as long as six months." Thus Wintrobe's standard text-book published in 1956. Experience, however, in the past few years has suggested to us that for many patients the prognosis is not in fact so gloomy; and that, with proper management, some patients may survive and pass eventually into remissions that are either complete or are at least compatible with normal life without the need for further blood-transfusions or other supporting treatment.

In 1958, two series of cases were published and among the patients were many who had survived for more than six months.

Mohler and Leavell (1958) reported a group of 50 patients of whom 43 had idiopathic aplastic anæmia; 13 were still living fifteen months to seventeen and a half years after the original diagnosis; and, of these, 3 had survived for more than five years, and 1 for more than ten. 30 had died—11 within the first year—but 14 had survived for more than three, 6 for more than five and 4 for more than ten years. Their patients varied in age from 8 to 82, but 58% were under 51. Treatment was mostly by blood-transfusion, repeated as necessary, and keeping to the " minimum compatible with the comfort of the patient ". Steroid treatment was given to 34 patients and benefited 15 of them.

Scott et al. (1958) reported a series of 39 patients: 17 of them had idiopathic aplastic anæmia, all but 3 being under 40 years old; the remaining 22 patients had aplastic anæmia secondary to various drugs. Splenectomy was used as treatment for 8 patients with idiopathic aplastic anæmia, and 6 of them showed partial or complete recovery. Of the remaining 2 patients, 1 died with pancytopenia and the other showed no improvement. Scott et al. are doubtful about the value of splenectomy, in spite of its apparent success. " An increase in the longevity of a group of splenectomized cases ", they say, " could not clearly be attributed to the operation, but may have resulted from selection of cases with a more favourable prognosis for operation."

In this paper, we report results with a group of 45 patients with uncomplicated idiopathic aplastic anæmia. 11 patients are alive and well from three months to ten years without further treatment; 14 lived for periods of four to forty-nine months, but another 20 died within three months of diagnosis. It is our object in this paper to show that, with proper management, perhaps a quarter of those diagnosed as having idiopathic aplastic anæmia can be maintained satisfactorily until they recover normal or almost normal health; approximately another quarter can be kept in reasonable clinical condition for some time.

Material

The diagnosis of idiopathic aplastic anæmia was confirmed by examination of the blood and the bone-marrow. The bone-marrow of all patients showed a reduction—often great—in the number of erythroblasts, granulocytes, and megakaryocytes, except in the 1 patient (case 7) who had pure red-cell aplasia. The blood-picture showed corresponding anæmia and granulocytopenia; but thrombocytopenia, although common, was less constant.

The patients had not to our knowledge been exposed to any drugs liable to cause this anæmia or marrow-depression, or to any sources of radiation. There was no evidence of increased blood destruction or of infiltrative disease, or of any other coincident blood disease, such as leukæmia, at any time in their course.

The patients can be divided into three groups:

Group 1.—11 patients who have survived, and who are not now receiving treatment.

Group 2.—14 patients who survived more than three months, but died subsequently.

Group 3.—20 patients who died within three months of being first diagnosed, with little or no evidence of remission.

Group 1.—In this group (table I), there are 6 male and 5 female patients; 8 of the 11 being under 40. The time since treatment was last needed varies from three months to ten years, and 8 of the 11 have now been more than two and a half years without treatment. The period of treatment needed before remission appeared has varied from five weeks to nearly three years; 5 of the patients needed more than fifteen months treatment. The volume of packed red cells transfused before remission varied from 3 to 104 pints. Half the patients were given supplementary steroid therapy—cortisone or prednisolone. In no less than 9 out of 11 patients the platelet-counts remained below 200,000 per c.mm., and, in 3 of them, below 100,000 per c.mm. long after remissions had occurred:

TABLE I—APLASTIC ANÆMIA PATIENTS IN REMISSION—NO LONGER RECEIVING TREATMENT

Case no.	Age (yr.)	Sex	Initial blood-count: Red cells (mill. per c.mm.)	Initial blood-count: White cells (thou. per c.mm.)	Initial blood-count: Polymorphs (%)	Initial blood-count: Platelets (thou. per c.mm.)	Weeks in hospital	Out-patient transfusions (mos.)	Hb (%)	Time since remission	Latest blood-count: Red cells (mill. per c.mm.)	Latest blood-count: White cells (thou. per c.mm.)	Latest blood-count: Polymorphs (%)	Latest blood-count: Platelets (thou. per c.mm.)	Pints of packed red cells (total)	Steroid treatment
1	6½	F	1·85	1·30	31	10	5	0	60–80	2½ yr.	3·84	3·15	36	101	6	Prednisolone 6 mos.
2	15	M	1·62	2·85	25	203	2	1	65–70	5½ yr.	5·05	7·90	71	280	3	None
3	23	M	1·59	1·30	23	24	6	34	60–70	4½ yr.	4·55	4·50	56	122	104	Cortisone 4 wk.
4	23	F	1·92	3·65	39	8	2	16	70–80	6 mos.	4·07	7·50	62	57	29	Prednisolone 12 mos.
5	25	F	1·87	3·50	27	38	8	3	55–75	4½ yr.	4·77	4·90	43	208	9	Cortisone 4 mos.
6	25	F	1·30	6·00	15	20	4	14	60–75	3 mos.	3·66	8·00	60	60	34	Prednisolone 3 mos.
7*	34	M	2·05	5·90	61	165	6	21	65–75	5½ yr.	5·46	6·90	62	125	81	None
8	36	M	1·44	2·90	25	43	5	2	60–70	6 yr.	5·16	8·42	71	140	5	A.C.T.H. 2 wk.
9	46	M	1·50	3·00	30	20	6	24	75–90	9½ yr.	4·14	5·00	36	73	40	None
10	63	M	1·62	9·00	53	15	0	5	60–80	1⁷/₁₂ yr.	4·29	6·65	53	109	7	None
11	64	F	1·08	2·80	38	205	2	25	70–80	9½ yr.	4·20	3·95	60	68	41	None

* Case of pure red-cell aplasia.

TABLE II—APLASTIC ANÆMIA—PATIENTS SURVIVING MORE THAN 3 MONTHS

Case no.	Age (yr.)	Sex	Initial blood-count: Red cells (mill. per c.mm.)	Initial blood-count: White cells (thou. per c.mm.)	Initial blood-count: Polymorphs (%)	Initial blood-count: Platelets (thou. per c.mm.)	Weeks in hospital	Outpatient transfusions (mos.)	Hb (%)	Pints of packed red cells (total)	Steroid treatment	Period of survival (mos.)	Cause of death
12*	5	F	1·92	2·85	49	11	5½	33	50–60	10	None	35	Hæmorrhage, pneumonia
13	12	F	1·63	2·20	14	23	13	6½	50–60	16	Cortisone	10½	Not known
14	18	F	1·54	5·30	38	11	12	None	50–60	16	Cortisone	4	General hæmorrhage
15	22	F	2·12	1·40	65	9	8	7	50–60	13	Prednisolone	9	General hæmorrhage
16	23	M	2·88	3·60	37	23	12	9	50–60	50	A.C.T.H., prednisolone	12	General hæmorrhage
17	25	F	2·17	5·70	22	19	18	2	55–65	41	Prednisolone	6½	General hæmorrhage
18	25	M	1·64	1·95	21	7	26	3½	45–55	62	Prednisolone	10	General hæmorrhage
19	38	M	2·43	7·30	6	3	13	7	45–55	36	None	10	General hæmorrhage
20	41	M	1·36	3·70	30	20	12	10	55–65	27	Cortisone	13	Cerebral hæmorrhage
21	48	F	2·19	2·60	41	280	13	21	80–90	51	None	24	Liver failure
22	53	M	1·26	2·00	63	208	9½	47	50–60	191	None	49	Not known
23	53	M	2·23	3·20	62	10	3	6	55–65	21	Prednisolone	7	Hæmorrhage, pneumonia
24	64	F	1·15	2·55	33	1	6	6	45–55	26	Prednisolone	7½	General hæmorrhage
25	72	F	1·37	7·70	70	154	8	27	55–65	50	Cortisone	29	General hæmorrhage

* Fanconi type with other congenital defects.

this does not seem to be important at these levels, and none of these patients have had hæmorrhages, or even petechiæ, in the skin.

Group 2.—Table II includes the cause of death, which was known in all cases except 2; hæmorrhage was the main cause of death in 11 patients. There were 6 male patients and 8 females; 7 of the 14 patients were less than 40. The periods of treatment until death varied from four months to forty-nine months; in 10 patients the periods did not exceed a year. The total volume of blood-transfusions given varied from 10 to 191 pints of packed red cells. Steroid treatment (cortisone or prednisolone) was given to 4 patients.

Group 3.—The details of the 20 patients in this group have not been listed since they show no unusual features. Table III shows the age and sex distribution; 9 out of the 20 were more than 40, 7 being over 50 years old; 8 were males and 12 females. Hæmorrhage was the cause of death of almost every patient.

Treatment and Management

The only effective treatment for most patients with aplastic anæmia is repeated blood-transfusion. At first, of course, our patients were treated in hospital after investigation had established the diagnosis. Since over half the patients require treatment over a long period, it is important not to keep them in hospital too long, both as regards the patient's morale and the economic use of hospital beds. As soon as a steady state has been reached and when it is clear that transfusion of 1 pint of packed red cells at weekly (or longer) intervals will keep the patient's hæmoglobin at a reasonable level, the patient is transferred to our outpatient transfusion clinic which we have organised specifically for the treatment of aplastic anæmia and other blood diseases needing repeated supporting blood-transfusions. By a " reasonable level " of hæmoglobin is meant 60–70% (9·0 to 10·5 g. per 100 ml.); at this level, the patient can carry on a reasonably normal life, continuing work—if not too heavy—between transfusions. If such a level can be maintained with fortnightly, or even longer, intervals between transfusions, the prognosis is much better. It will be seen from tables I and II that, on the whole, a higher level of hæmoglobin was maintained in the patients who eventually went into remission than in those who only survived for longer than three months.

TABLE III—APLASTIC ANÆMIA—PATIENTS SURVIVING LESS THAN 3 MONTHS

Age group (yr.)	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	Total
Male	0	0	0	2	2	2	1	1	8
Female	2	3	2	2	0	1	2	0	12
Total	2	3	2	4	2	3	3	1	20

The outpatient transfusion clinic is organised as follows:

A list is prepared every Thursday of outpatient blood-transfusions arranged for the following week, and the necessary quantities and types of blood are ordered from the department of clinical pathology who obtain the blood from the regional bank. We also collect regular quantities of suitable blood from our large series of patients with polycythæmia. Serum and cells for cross-matching have been supplied either before the patients left the ward, or by taking blood when the patients came for the previous transfusions. On the morning of the transfusion, the red cells are packed and the packed cells delivered to the department before 11 A.M. The patients are instructed to arrive about 11 A.M. and are made comfortable on a bed. The department has a warm light room with three beds in it for the purpose. The transfusions take three to three and a half hours to complete. We carry out about 500 transfusions a year. Transfusion reactions are unusual, and rarely more than transient; on only two occasions in the past five years has a patient had to be detained overnight.

Since the patient is dependent for his life on the state of his veins—and may be so for two years or more—great care is taken in the preparation and setting up of the transfusion apparatus.

Instead of the standard Ministry of Health giving-sets we use a composite set of our own design, which is cleaned, prepared, and sterilised by our own staff (Wilkinson et al. 1956). This set allows either saline or blood to be infused, and the tubes from the two bottles lead, via a connecting Y-piece, into a filter drip-chamber containing a filter of stainless-steel mesh; such a filter is needed when packed red cells are being regularly used because the customary plastic filters tend to choke. The tube from the filter/drip-chamber leads to a ribbed plastic end-piece which fits into the usual Luer needle-hub. All the connecting tubing is of latex or of silicone rubber. A no. 1 serum needle is used for giving the transfusion; sometimes, if veins are small, a no. 2 may be substituted.

For setting up the transfusion, the apparatus is filled with saline which is allowed to run slowly into a bowl. The no. 1 needle is fitted to a 5 ml. syringe and inserted into the vein; when it is properly in place and blood can be easily withdrawn, a sample is taken for the next cross-matching; the syringe is then detached and the plastic end-piece of the transfusion set inserted into the needle-hub; when the saline is running freely, blood is turned on and the saline turned off. When all the blood has been transfused, the system is cleared by allowing saline to run again for a few minutes; this helps to prevent a hæmatoma forming at the transfusion site.

In addition to blood-transfusion, we may also give other supplementary treatment (particularly steroids) and, in women, a non-virilising androgen. Steroid treatment, which today means prednisone or prednisolone in doses from 50 to 100 mg. daily, does seem to diminish bleeding from skin and mucous membranes, possibly by increasing capillary resistance. Our experience provides no definite evidence that steroids can induce a remission. The dose of 50–100 mg. daily should not be continued for more than four weeks and, if a maintenance dose is given—say, to reduce purpura—15 mg. daily is the maximum dose we use.

In women in the reproductive period of life, the great danger is menorrhagia; this has often proved the most difficult blood-loss to control, and it must be controlled if the treatment is to be carried on for months or years before remission of the anæmia. Here, endocrine treatment has proved helpful—especially the use of non-virilising androgens. Fluoxymesterone, in a dose of 5 mg. by mouth daily at first, later reducing to 2 mg., if possible, seems to be the best preparation at present.

Discussion

Idiopathic aplastic anæmia is still a serious and dangerous disease, and 45% of our patients were dead within three months of the time they were first seen. Nevertheless, when 22% remit permanently and a further 31% survive for more than six months, it is clearly worth while making an effort to treat these patients as efficiently and persistently as possible from the beginning. Some guide to prognosis can be obtained from the early response to treatment. Hæmorrhage is the main danger; if this has never been serious, or if it stops within two or three weeks after the commencement of treatment with regular steroids and blood-transfusions, the prognosis is more hopeful. If, on the other hand, hæmorrhage continues unchecked, and particularly if there is frequent melæna, persistent menorrhagia, or retinal hæmorrhages, the outlook is bad. Another useful guide is the frequency of blood-transfusion needed for maintenance. Most of these patients were seriously anæmic when first seen, 18 out of the 25 patients in groups 1 and 2 having a red-cell count of less than 2 million per c.mm. Consequently, quite large transfusions were needed initially to raise their hæmoglobin to the desired 60–70% level. But after this, in the absence of severe hæmorrhage, it should be possible to maintain this level with transfusions of 1 pint of packed red cells given not more often than once fortnightly. If transfusions have to be given more often, the outlook is not good; this stage is sometimes reached after a long time on fortnightly maintenance, but sometimes is present from the start. Attendance for a weekly outpatient blood-transfusion is a strain for both the patient and the clinic, but the effort is nearly always worth making. Often the patient may be kept at work, and the possibility of a remission can never be entirely excluded, although table I shows that in only 1 patient of the 11 in group 1 was the appearance of the remission delayed much beyond two years after the beginning of treatment.

Considerable patience is needed by both the patient and doctor in the treatment of aplastic anæmia, but many of the results obtained by ourselves and by others have been very rewarding. This is also true in some forms of toxic aplastic anæmia—for example, Lane (1952) had 5 patients with aplastic anæmia due to exposure to trinitrotoluene (T.N.T.), all of whom recovered when treated with repeated blood-transfusions.

Table I shows that 1 of our patients needed 81 transfusions, and another 104, before remissions occurred, but both these patients are now leading normal active lives; on the other hand, table II shows that death took place after 62 transfusions had been given during ten months to a man of 25; while another man, aged 53, lived for forty-nine months, receiving 191 transfusions.

The key to successful management of aplastic anæmia is undoubtedly the provision of *regular* blood-transfusions at sufficiently frequent intervals. The alternative is to give transfusion only when the hæmoglobin falls below some arbitrary level—say, 50%; in our experience, this gives poorer results and has a disastrous effect on the morale of the patient. We have been surprised how well patients adapt themselves to the fortnightly transfusion regimen. With the alternative method every visit to the clinic is a cause for apprehension because the blood-count may have fallen, and transfusion may be needed.

Summary

In a series of 45 patients with idiopathic aplastic anæmia, 11 remitted completely and have remained alive and well without treatment for from three months to ten years; 14 survived for more than three months but died later, and 20 died within three months of diagnosis.

The commonest cause of death is hæmorrhage in some form, and patients who have been on treatment but have not remitted have survived for from four to forty-nine months.

The key to effective management and treatment of aplastic anæmia is to give repeated blood-transfusions to keep the hæmoglobin level, if possible, between 60–70%. The transfusions should be given at *regular* and frequent intervals; once a fortnight suffices for most patients. The transfusions have been given without the need for admission as inpatients, and the organisation of a very successful outpatient transfusion clinic is briefly described.

Prednisolone to reduce hæmorrhage and, in women, fluoxymesterone to control menorrhagia, have been found to be very useful adjuvants to treatment.

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". . . patients are fearful, suspicious, doubtful, sensitive, anxious, and often lonely. Trying to appear calm and unworried, they often joke and seem to appear gay. Underneath, however, they are deeply worried. When in this state of mind their greatest need is to feel close to those around them. Each person in the hospital setting becomes important to the patient, because he believes each one knows something about him. Whether it be the cleanup girl, an intern, a nurse, or an attending physician, the patient needs to identify strongly with optimistic, kind, understanding, and supportive people. *There is no more effective medicine than kindness nor is there any substitute for it.* It is an essential ingredient in all human relationships. When one is frightened and lonely, a cold, disinterested and indifferent attitude on the part of attending personnel can be devastating."
—Dr. THOMAS E. RARDIN, *J. Amer. med. Ass.* 1960, **174**, 1254.

MECHANICAL VENTILATION FOR ACUTE RESPIRATORY FAILURE IN DIFFUSE CHRONIC LUNG DISEASE

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IN advanced diffuse chronic lung diseases acute respiratory infection, overdose of morphine, operations, &c., may cause dangerous episodes of acute respiratory failure. The clinical picture is one of severe dyspnœa, cyanosis, confusion, drowsiness or coma, and a varying degree of airway obstruction due to accumulation of secretions. There may be congestive heart-failure and irregular muscle-twitching. Blood-pressure is often high, but severe hypotension may supervene.

In these acute respiratory crises the oxygen supply of the organism must be improved. This is often done by administration of oxygen and antibiotics, removal of secretions by nasopharyngeal or tracheal suction after massage of the chest, and treatment of cardiac failure. Sometimes this conservative regime fails, because hypoxia cannot be corrected without depressing ventilation dangerously, or because a free airway cannot be maintained. Several recent reports show that tracheotomy followed by artificial ventilation—or ventilation alone—may be life-saving in this situation. A total of 42 cases have been published; and 31 of these patients survived (Bourtourline-Young and Whittenberger 1951, Stone et al. 1953, Chermiak 1953, Lovejoy et al. 1954, Bjørneboe et al. 1955, Austen et al. 1957, Mollaret et al. 1958a, 1958b, Davidson 1959, Mortensen 1959).

We discuss here the selection of cases for tracheotomy and artificial ventilation, based on experience with 23 consecutive cases from 1955 to 1960.

Technique

After tracheotomy at 2nd or 3rd ring—often without anæsthetics—a rubber cuff-tube (Rüsch) was inserted, and ventilation with 6–10 litres per minute of a high-oxygen mixture was administered using a Lundia intermittent-positive/negative-pressure respirator giving a constant minute ventilation at a constant rate. Usually the arterial oxygen saturation became normal, and the patients regained consciousness after a few hours. During the first one or two days ventilation was gradually increased, and arterial carbon-dioxide tension (pCO_2) often became normal. Full return to spontaneous respiration took one to two weeks, starting with ten to fifteen minutes per hour out of the respirator. The accompanying figure illustrates the course in a typical case.

Blood for gas analysis was obtained by puncture of the femoral artery. Oxygen saturation was measured by means of Brinkman's hæmoreflector (Zijlstra 1953). Total carbon-dioxide content was determined manometrically (Van Slyke and Neill 1924). Arterial pH was measured with glass electrode and potentiometer. pCO_2 was calculated from the arterial pH and the total carbon-dioxide content (Astrup 1954).

Material

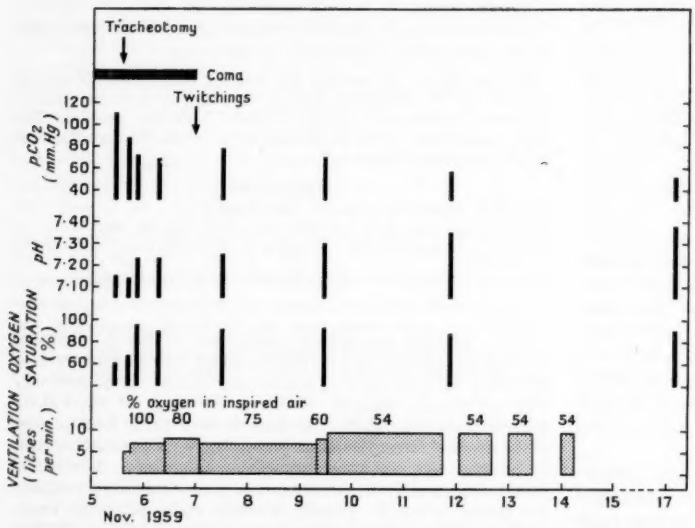
4 women and 19 men, with an average age of 56 (44–69), were ventilated with the Lundia respirator for an average of twenty-four days (range, twelve hours to one hundred and twenty-six days).

17 patients had chronic bronchitis. In 3 the chronic ventilatory disability was due to pulmonary fibrosis after tuberculosis; 3 had kyphoscoliosis. The duration of chronic lung disease cannot be stated precisely—the duration of the pulmonary symptoms had been anything from "a few years" to approximately thirty-five.

The commonest causes of the respiratory crisis were pneumonia, influenza, and acute bronchitis. In other patients, the precipitating factor was an overdose of morphine, abdominal surgery, acute pancreatitis, or diabetic precoma.

16 were in coma immediately before tracheotomy; the remaining 7 were semicomatose. In 14 patients large amounts of secretions had accumulated in the airway, 10 had congestive heart-failure, and, in 11, electrocardiography showed right ventricular strain. The average arterial pCO_2 was 89 mm. Hg just before tracheotomy (range, 67–114 mm.); pH averaged 7·22 (7·03–7·37). In the 5 patients who were without extra supply of oxygen during sampling the arterial oxygen saturation averaged 54% (range 43–64%).

5 patients were ventilated in a tank respirator (Dräeger) for some days before tracheotomy, but this treatment proved inefficient because of airway obstruction.



Data on artificial ventilation, arterial pCO_2, pH, and oxygen saturation before, during, and after artificial ventilation in pulmonary fibrosis following tuberculosis.

Severe purulent bronchitis of a few days duration caused the acute respiratory failure. The samples for analysis of arterial blood on Nov. 5 and 11 were taken while the patient was breathing spontaneously with extra oxygen. The patient was breathing room air without extra oxygen on Nov. 17.

Results

15 patients survived the crisis and 8 died. In those who survived, the mechanical ventilation lasted thirteen days on the average (range, twelve hours to thirty-two days). In those who died, the corresponding figures were forty-four days (twelve hours to one hundred and twenty-six days). 1 patient died twelve hours after admission from lobar pneumonia with

hyperthermia and shock. Another patient died from shock following acute pancreatitis. The other 6 died from irreversible cardiopulmonary failure sixteen to one hundred and forty-seven days after admission.

On discharge from hospital analyses of arterial blood showed: oxygen saturation 82% (range, 71–96%), pCO_2 44 mm. Hg (range, 30–56 mm.), and pH 7·41 (range, 7·31–7·49).

At a follow-up examination two to thirty months (average nine months) after discharge from hospital,

TABLE I—MEAN VALUES FOR ARTERIAL pCO_2 AND pH IMMEDIATELY BEFORE TRACHEOTOMY IN SURVIVING PATIENTS AND IN PATIENTS WHO DIED

—	Survived (15 patients)	Died (8 patients)	P
pCO_2 (mm. Hg):	92·0	83·0	>0·1
S.E. of mean	4·7	3·2	
pH:	7·21	7·24	>0·1
S.E. of mean	0·026	0·035	

S.E. = standard error.

5 patients were back at work; 7 were out of work, but capable of looking after themselves; and 1 was still in hospital on spontaneous respiration without extra oxygen. Finally, 2 had died owing to relapses, four and eight months after discharge.

Complications were few. As could be expected there was nearly always a minor fall in blood-pressure at the beginning of mechanical ventilation; in only 1 patient did shock develop. This disappeared after reduction of ventilation, and a transfusion of blood.

In 1 patient, a man aged 67 with chronic bronchitis of fifteen to twenty years' duration, congestive heart-failure, influenza, bronchopneumoniæ, and liver cirrhosis, a tracheo-œsophageal fistula developed owing to pressure from the cuff-tube after fifty-five days' ventilation. He died fifteen days later from progressive pulmonary infection and circulatory collapse.

Discussion

It is highly probable—though difficult to prove—that most of the 15 who survived would have died in the acute phase had tracheotomy and artificial ventilation not been undertaken. On the other hand, several patients died despite the intensive treatment. Therefore criteria to determine which patients could be expected to benefit from the treatment would be valuable. We have analysed the series by correlating the results with some biochemical, anamnestic, and clinical characteristics.

TABLE II—ANAMNESTIC AND CLINICAL DATA CORRELATED TO MORTALITY

—	No. of patients	Mortality	P
Mental state:			
Coma	16	4/16	>0·1
Semicoma	7	4/7	
Congestive heart-failure:			
Present	10	3/10	>0·1
Absent	13	5/13	
Electrocardiogram:			
Right strain	11	4/11	>0·1
No right strain	12	4/12	
Secretions in airways:			
Large amounts	14	5/14	>0·1
Moderate	9	3/9	
Physical capacity:			
A. Capable to work	12	1/12	A versus C P<0·01
B. Out of work, able to manage personal requirements	5	2/5	A versus B P>0·1
C. Unable to leave bed or room	6	5/6	B versus C P>0·1

$$t = \frac{p_1 - p_2}{\sqrt{p(1-p)\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}, \text{ where } p_1 = \frac{x_1}{n_1} \text{ and } p = \frac{x_1 + x_2}{n_1 + n_2} \text{ (Hald 1957).}$$

Table I shows that knowledge of the pretreatment values for arterial pCO_2 and pH is no help in assessing the outcome, there being no significant difference in these parameters between the group of patients who survived and the group of patients who died (" t "-test).

Table II gives the frequency of some other data relevant to the outcome. As would be expected, the prognosis was much better in patients who had been able to work (A) all the time up to the crisis than in those whose respiratory reserve was very slight (C). Nothing can be concluded from the results in the intermediate group (B). The clinical data show that there was no significant difference in mortality whether coma, congestive heart-failure, right ventricular strain, or large amounts of secretions were present or not. Evidently these symptoms are of no prognostic value.

This implies that the chance of tiding patients with diffuse chronic lung disease over an episode of life-threatening respiratory failure—and of obtaining a reasonable recovery—with the treatment described is fair, when the case-history is indicative of a pulmonary reserve. Such treatment, therefore, is clearly indicated for these cases. In patients without pulmonary reserve, the result of the active treatment is hardly better than that of an ordinary conservative regime. The very alarming acute clinical picture and the severe biochemical changes, demanding tracheotomy and artificial ventilation, are the same in patients with pulmonary reserve as in those without.

Summary

23 consecutive cases of diffuse chronic lung disease with lifethreatening respiratory failure were treated by tracheotomy and mechanical ventilation.

Analysis of the cases shows that the outcome is good when the case-history indicates the presence of a pulmonary reserve, even if the clinical condition and biochemical changes are alarming when treatment is started. When no pulmonary reserve is present, the results are hardly better than those of ordinary conservative treatment.

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A SIMPLE LABORATORY TEST TO DISTINGUISH THE VIRUS OF SMALLPOX FROM THAT OF ALASTRIM

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WE here describe a simple way of distinguishing the virus of smallpox from that of alastrim by inoculating the chick chorioallantois, and incubating the eggs at temperatures above the optimum for virus growth.

In a mild case of variola, the clinical differentiation between smallpox and alastrim can be made with confidence only after secondary cases have arisen. But in non-endemic areas it is highly desirable to know earlier the type of variola that has entered the community.

Our method is a simplification of that proposed by Dinger in 1956. He showed that smallpox virus could be recovered from chick chorioallantoic membranes 5 days after inoculation, whereas this could not regularly be done when alastrim virus was inoculated. Helbert (1957) found that smallpox virus was more pathogenic for the chick embryo than was alastrim virus; this was measured both by mortality-rates and by the amount of virus that could be recovered from the embryo liver after virus had been inoculated on to the chorioallantois. The validity of Helbert's method was confirmed by Andres et al. (1958).

Method

Virus Strains Tested

Alastrim.—Strains A1–A5 were obtained from the outbreak in Rochdale (Innes 1953); strains A6–A9 from the epidemic in The Hague (Blomhert 1955) were made available through the kindness of Prof. J. E. Dinger; and strain A10 was the strain J, used by McCarthy and Downie in 1948. Strain A11 was the strain of virus isolated from case 19 of Downie and Dumbell (1947); the reasons for classing it as alastrim will be discussed below.

Smallpox.—Strain S1 was isolated from a case in the Middlesex outbreak (Bradley et al. 1946); S2 and S3 were from the outbreak on Merseyside in 1946 (Peirce 1947); S4 was the strain from case 8 listed by Downie and Dumbell (1947); S5 was isolated from a case in Staffordshire (Smith 1948); strain S6 was isolated from case 7 of the Glasgow epidemic (Laidlaw and Horne 1950); strains S7–S9 were isolated from fatal cases (7, 12, and 13 described by Murphy 1954) in the Pennines epidemic (Lyons and Dixon 1953); strain S10 was isolated from case T.L. on Merseyside in 1958 (Peirce et al. 1958); and strains S11–S14 were isolated from cases of variola major in Entebbe in 1956 (S11), Bombay in 1958 (S12), and Madras in 1960 (S13 and S14).

Most of these strains had been dried from the frozen state after the first or second egg passage, soon after isolation, and all were tested in the second to seventh egg pass. In addition, strain S4 was tested in its seventy-first egg pass. Strains A1 and S1 are those designated as the type strains of alastrim and variola respectively (Fenner and Burnet 1957).

Technique

Eggs from a commercial supplier were preincubated at 38°C in a 'Westernette' incubator with air circulation, and were rocked hourly during the first 12 days; on the 12th day they were candled, and prepared for inoculation on the chorioallantois. After inoculation, the eggs were placed in incubators fitted with internal fans to keep the internal temperature uniform. Temperatures were measured by thermometers placed close to the eggs and were recorded three times a day. The most satisfactory incubator for the purpose was a chamber warmed by a fan heater-unit. The heater, but not the fan, was operated through a 'Sunvic' TR7 thermostat and relay. Because the chamber had a fairly high rate of heat loss, the heater was switched off and on at about 5-minute intervals, and the air temperature around the egg racks underwent regular fluctuations of ±0·25°C. This was a satisfactory margin for the experiments. Water-jacketed incubators were also used in some of the experiments, care being taken to keep a frequent check on the temperature, and to have the incubator open for the shortest possible time.

Results

Preliminary experiments were made with one strain each of smallpox and alastrim virus (S4 and A1). Groups of eggs were inoculated on the chorioallantois with enough virus to produce about 100 lesions if the eggs were incubated at the optimal temperature for virus growth (35–36°C). The effect of temperatures higher than optimal was tested, and under these conditions smallpox and alastrim behaved differently, as can be seen from table I. Alastrim virus gave no pocks at temperatures over 38°C, but at temperatures up to 38·5°C, the strain of smallpox virus gave characteristic pocks although they were fewer in number and slightly smaller than the same virus concentration gave at 35°C. All experiments included at least one strain each of smallpox and alastrim as an internal control on the validity. If the dose of alastrim virus was increased a hundredfold to the equivalent of 10,000 pock-forming units there were still no visible lesions after 48 or 72 hours' incubation at 38–38·5°C. Furthermore, if such negative membranes were excised after 48 hours and extracted in buffer, the extracts did not give specific lesions when inoculated on to the chorioallantois of eggs and incubated at 35°C. The failure of alastrim virus to produce pocks in eggs incubated at 38–38·5°C was not due to inactivation of the virus before adsorption. When a group of eggs, inoculated with alastrim virus, was incubated for 12 hours at 38·25°C (sufficient to cover adsorption time), and then transferred to an incubator at 35°C for a further 48 hours, just as many specific pocks were seen as in eggs incubated throughout the 60 hours at 35°C.

TABLE I—POCK-COUNTS ON EGGS INOCULATED WITH SMALLPOX OR ALASTRIM VIRUS AND INCUBATED FOR 3 DAYS AT VARIOUS TEMPERATURES

Incubator mean temperature (°C±0·25)	Pock-counts on individual eggs inoculated with	
	Smallpox strain S4	Alastrim strain A1
35·25	103, 98, 75, 55	130, 125, 119, 98
37·75	Not tested	10, 9, 3, 0
38·25	51, 46, 44, 37	0, 0, 0, 0
38·75	0, 0, 0, 0	Not tested

In view of the potential usefulness of this test, the investigation was extended to all those strains of smallpox and alastrim viruses listed above. The results are summarised in table II, which shows a clear distinction between all the smallpox strains and alastrim strains A1–A10.

Alastrim strain A11 requires further comment. This strain was regarded as variola major until it was checked for temperature sensitivity in our investigation. In this character it

TABLE II—POCK-COUNTS IN EGGS INCUBATED AT 35° AND 38·25°C

Smallpox				Alastrim			
Strain no.	Egg pass	Pock-count at 35°C	Pock-count at 38·25°C	Strain no.	Egg pass	Pock-count at 35°C	Pock-count at 38·25°C
S1	1st	55	20	A1	2nd	67	0
S2	2nd	91	77	A2	7th	174	0
S3	3rd	73	43	A3	7th	125	0
S4	7th	83	44	A4	5th	35	0
	71st	60	25	A5	5th	110	0
S5	2nd	139	48	A6	2nd	300	0
S6	4th	61	40	A7	2nd	130	0
S7	5th	200	87	A8	3rd	40	0
S8	7th	164	72	A9	3rd	31	0
S9	5th	72	34	A10	5th	96	0
S10	1st	82	15	A11	2nd	62	0
S11	5th	124	70	..	..	..	..
S12	1st	40	30	..	..	..	..
S13	1st	187	76	..	..	..	..
S14	1st	39	15	..	..	..	..

Pock-counts quoted are the average counts from 3–5 membranes from eggs inoculated with a suitable dilution of virus suspension.

TABLE III—MORTALITY OF CHICK EMBRYOS INFECTED WITH VIRUS STRAIN A11 COMPARED WITH KNOWN SMALLPOX AND ALASTRIM VIRUSES

Virus	Strain	Virus dose in pock forming	Number of eggs	Cumulative deaths on day						
				1	2	3	4	5	6	7
Smallpox	S4	10^6	6	0	0	1	6	..	..	..
Alastrim	A2	10^6	6	0	0	0	0	2	4	5
	All	10^6	6	0	0	0	0	2	5	6
Smallpox	S4	10^5	6	0	0	0	6	..	..	..
Alastrim	A2	10^5	6	0	0	0	0	2	4	5
	A11	10^5	6	0	0	0	0	3	5	5

was so typical of alastrim strains that the virus was examined by Helbert's method for chick-embryo pathogenicity with the results shown in table III. Here again the results are typical of alastrim. This virus was isolated in 1945 from a case of mild variola in a young private returned to this country by air from Naples. He was said never to have been vaccinated, and the physician in charge had commented that the patient was never as ill as might have been expected from the extent of his rash. One secondary case resulted: the patient's sister became ill 11 days after her brother. She was vaccinated for the first time 8 days before the onset of her illness, and she had a typical primary take. Her rash was fairly extensive, but her temperature was never high and had returned to normal within 6 days. These clinical details, given to us by Prof. A. W. Downie, are consistent with a diagnosis of alastrim, and in both laboratory tests the virus has behaved as such.

Discussion

The reasons why two such closely related viruses as smallpox and alastrim should differ so much in their sensitivity to a slight rise in the host temperature are of obvious interest. The effect of temperature on the growth of smallpox virus in the chick chorioallantois was considered by Hahon et al. (1958). We know that sensitivity to host temperature is a feature of some other pox viruses. In 1936 Burnet and Lush noted that ectromelia virus would not grow in the chick chorioallantois if the eggs were incubated at more than 39°C. Recently Porterfield and Allison (1960) have shown that, in tissue culture, ectromelia will not form plaques at 37 or 39°C. The relation of temperature to the growth of vaccinia in the chick embryo was intensively studied by Siim (1949), who found a reduction of mortality-rate as the host temperature was increased. This phenomenon has also been described for fibroma and myxoma viruses, first by Thompson (1938) and more recently by Marshall (1959). Marshall also noted that rabbit-pox virus would grow on the chick chorioallantois at 39°C and probably at 40°C.

Bedson and Dumbell (1961) have compared the sensitivity of viruses of the variola-vaccinia group with variations in the temperature of the chick-embryo host, and have related this to the virulence for the chick embryo of the viruses studied. A more detailed investigation of the temperature inhibition of variola virus is now in progress; but, until the operative mechanism has been revealed, it is pointless to speculate about the relevance of the phenomenon we describe in this paper to the virulence of smallpox and alastrim in man. The body of information on the relation of host temperature to the behaviour of other infecting organisms, which is too extensive to quote, has recently been reviewed by Bennett and Nicastri (1960). Some virulent strains of bacteria and viruses are able to grow at higher temperatures than the respective avirulent strains, and some experimental infections have been reduced in severity or aborted by raising the temperature of the host. But in the present state of knowledge one should be cautious about formulating any general hypothesis of the importance of host temperature in non-specific resistance to infection.

The previous work of Dinger (1956) and Helbert (1957) provided laboratory procedures for differentiating between virus strains from smallpox and alastrim. Our method seems to be as reliable as either of these, and to be preferable because of its simplicity and greater rapidity.

Summary

1. Smallpox virus will produce lesions on the chorioallantois of chick embryos kept in an incubator at 38–38·5°C for 2–3 days after inoculation. This has been confirmed for all fourteen smallpox-virus strains tested.

2. Alastrim virus will not produce lesions on the chick chorioallantois under the above conditions. This has been confirmed for ten strains of alastrim.

3. On the basis of agreement between this test and Helbert's (1957) test an additional strain of virus (A11) has been labelled alastrim; the clinical picture was consonant with this.

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STUDIES OF HEPATIC FUNCTION DURING METHANDIENONE THERAPY

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THE anabolic action of testosterone and its derivatives can be of considerable therapeutic value in many wasting illnesses and some types of osteoporosis. Androgens may also restrain the growth of certain breast cancers, and some of these steroids and closely related compounds are being extensively tested as fertility-controlling agents (Rock et al. 1960). Prolonged administration is often needed, with the consequent problem of unwanted virilising effects. Removal of the C19 methyl group from testosterone, producing the 19-nor configuration (Birch 1950), has resulted in compounds with unimpaired anabolic action but much reduced virilising activity. Nandrolone (' Durabolin ') is an example of such a drug. But it must be given by injection. The substitution of an alkyl group in the 17α position of the steroid nucleus confers activity when the substance is given by mouth (Miescher and Tschopp 1938). Norethandrolone (' Nilevar ') is an example of an orally active anabolic nor-steroid with reduced virilising action.

Methandienone (' Dianabol '), a Δ^1-17-α-methyl testosterone, is not a nortestosterone. It is active when given by mouth, and has little virilising effect, as first shown by Desaulles et al. (1959) in the rat. We have confirmed these results in man (Wynn and Landon 1960). Against the greater convenience of oral activity must be set one disadvantage, shown to variable extent by all the 17α-alkyl substituted derivatives of testosterone so far tested—namely, an effect upon liver function (Foss and Simpson 1959). The subject warrants wider attention with the increasing use of anabolic steroids now that separation of anabolic from virilising effects is possible, and because of the other uses of these and related steroids —e.g., as progestational agents and as inhibitors of ovulation. We have studied the hepatic effects of methandienone in thirty patients taking this drug.

Patients and Methods

The patients studied, and the dose and length of administration of methandienone, are shown in table I. Long-continued therapy was sometimes required.

The main indications for giving methandienone were malnutrition or cachexia, which was slow to respond to ordinary dietary measures (cases 3, 8–11, 13–15, 19–21, 23, and 28–30); osteoporosis (cases 1 and 2); to counteract the metabolic complications of prolonged corticosteroid therapy (cases 6, 17, and 31–33); in the treatment of Cushing's syndrome (cases 5, 16, and 24); and to reduce urinary calcium excretion (cases 4, 12, and 18). One patient (case 7) was given the drug, together with triiodothyronine, in an effort to reduce severe Raynaud's attacks in the hands and feet which were unaffected by sympathectomy (Peacock 1960). One patient (case 22) had Addison's disease. The patients' ages ranged from 14 to 83 years. Eleven were men and nineteen were women.

The dose of methandienone varied from 5 to 100 mg. daily, and the studies lasted from 7 to 260 days. As a result of our later studies we now know that the largest doses used are about four times larger than is necessary to produce a satisfactory therapeutic response.

Assessment of hepatic toxicity was based upon:

Clinical examination, including a record of the patient's symptoms, evidence of jaundice, and frequent examination of the abdomen for hepatic enlargement or tenderness, or splenic enlargement.

Repeated liver-function tests, including measurement of serum-bilirubin, alkaline-phosphatase activity, thymol-turbidity and flocculation tests, total serum-protein, albumin/globulin (A/G) ratio, electrophoretic studies, serum glutamic-oxalacetic transaminase (S.G.O.T.) levels, the retention of bromsulphthalein (B.S.P.) 45 minutes after injection (5 mg. B.S.P. per kg. body-weight), and repeated examination of the urine for abnormal bilirubin, urobilinogen, and urinary aminoacid excretion.

The estimations were performed while the patients were in hospital at fortnightly intervals at least, and then at each outpatient visit. Some patients were transferred to us from other departments and, in some of these, early liver-function tests are not available.

Results

None of the patients developed clinical evidence of disordered liver function. No patient complained of anorexia, pain in the right hypochondrium, itching or weight loss, and none showed jaundice or increase in the size of the liver or spleen.

Effects of Methandienone on Liver-function Tests

Bilirubin levels.—In twenty-nine patients the serum-bilirubin did not alter significantly while the patients were given methandienone.

TABLE I—CLINICAL SUMMARY OF THE THIRTY PATIENTS STUDIED

Case no.	Sex	Age (yr.)	Diagnosis	Dose and length of methandienone therapy (mg. per day)	Days of methandienone therapy during which liver-function tests were studied
1	F	60	Acute intermittent porphyria	(*a*) 50 mg. for 33 days	(*a*) 33†
			Postmenopausal osteoporosis	(*b*) 25 mg. for 160 days*	(*b*) 160
2	M	28	Acute idiopathic osteoporosis	100 mg. for 26 days, and 75 mg. for 198 days*	176
3	F	50	Acute glomerulonephritis; cachexia	25 mg. for 70 days	70
4	F	37	Renal tubular acidosis with nephrocalcinosis	25 mg. for 200 days*	91
5	F	28	Cushing's syndrome; peptic ulceration (recurrence of Cushing's syndrome after bilateral adrenalectomy 8 years before; adrenal tissue not found at laparotomy)	(*a*) 50 mg. for 27 days, 100 mg. for 12 days, 50 mg. for 12 days, 12·5 mg. for 29 days, and 30 mg. for 130 days	(*a*) 210†
				(*b*) 50 mg. for 9 days	(*b*) 9
6	F	60	Systemic lupus erythematosus on prednisone; K-losing pyelonephritis; cachexia	50 mg. for 40 days, 12·5 mg. for 80 days, and 25 mg. for 40 days*	160
7	F	28	Severe Reynaud's syndrome	20 mg. for 210 days*	204
8	M	53	Pancreatic steatorrhœa; malnutrition	50 mg. for 65 days*	65
9	F	43	Pyelonephritis; anorexia nervosa	25 mg. for 260 days*	260
10	F	75	Postgastrectomy diarrhœa; malnutrition	(*a*) 25 mg. for 33 days	(*a*) 33†
				(*b*) 25 mg. for 201 days*	(*b*) 201
11	F	51	Chronic pyelonephritis; malnutrition	50 mg. for 7 days, and 25 mg. for 44 days	51
12	M	21	Idiopathic hypercalcuria	50 mg. for 14 days	14
13	F	26	Septic abortion; acute tubular necrosis; hepatotoxic jaundice; persistent pelvic infection; cachexia	25 mg. for 22 days	22
14	F	40	Chronic malnutrition	50 mg. for 15 days	15
15	F	62	Carcinoma of breast, with bone and liver metastases	25 mg. for 10 days	10
16	F	57	Cushing's syndrome; carcinoma of adrenal cortex with liver metastases	50 mg. for 10 days	10
17	F	47	Chronic bronchitis; asthma and aspergillosis (having prednisone); malnutrition	50 mg. for 43 days, and 25 mg. for 60 days*	103
18	M	24	Idiopathic hypercalcuria	50 mg. for 10 days	10
19	F	83	Ischæmia; peripheral arterial disease; malnutrition	50 mg. for 41 days	41
20	M	70	Prostatomegaly; pyelonephritis; malnutrition	100 mg. for 6 days, and 50 mg. for 19 days	25
21	M	50	Partial gastrectomy; malnutrition	50 mg. for 16 days	16
22	M	28	Addison's disease	25 mg. for 16 days	16
23	M	30	Idiopathic steatorrhœa; malnutrition	50 mg. for 98 days*	98
24	M	21	Cushing's syndrome	100 mg. for 22 days	22
(25, 26, and 27 not included because insufficient liver-function tests were performed)					
28	M	14	Anorexia nervosa	10 mg. for 8 days, 15 mg. for 12 days, and 20 mg. for 6 days	26
29	M	39	Anorexia nervosa	20 mg. for 16 days	16
30	F	26	Anorexia nervosa	20 mg. for 10 days, 15 mg. for 10 days, 10 mg. for 2 days, and 5 mg. for 6 days	34
31	F	44	Asthma (having triamcinolone)	50 mg. for 14 days, and 25 mg. for 82 days*	96
32	F	52	Asthma (having triamcinolone)	25 mg. for 100 days*	100
33	M	62	Asthma and chronic bronchitis; osteoporosis (having prednisone)	25 mg. for 33 days*	33

* Still having methandienone at time of present study. † Two separate periods of study, separated by at least a month.

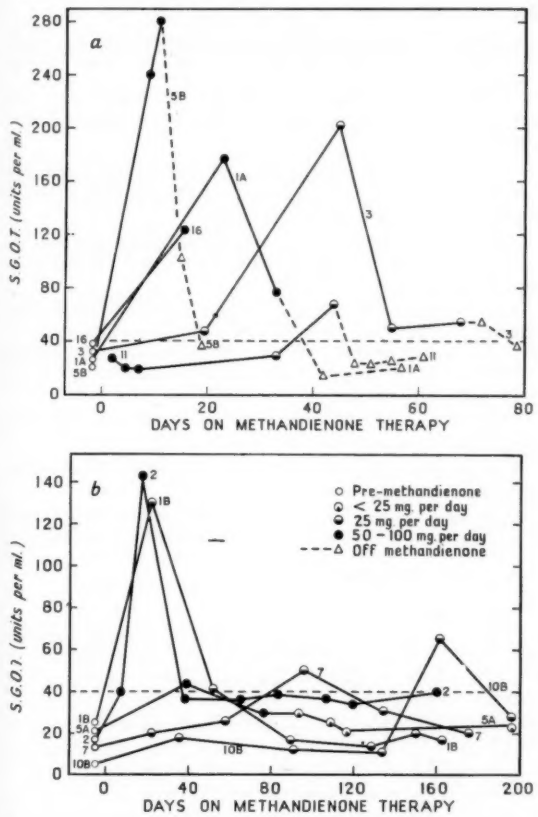
In case 7 the serum-bilirubin was 1·2 mg. per 100 ml. before methandienone, and 2·0 mg. 57 days after methandienone 20 mg. daily, dropping to 0·4 mg. after 95 days on the drug, and remaining normal since then.

Alkaline phosphatase was unaffected in all patients except case 7, in whom it rose from 9 to 16·2 King-Armstrong units after 57 days on methandienone, 20 mg. daily. In later estimations this has returned to normal.

Thymol-turbidity and flocculation were unaffected, with the possible exception of case 5 in whom thymol-turbidity was occasionally as high as 4 units.

Serum-protein, A/G ratio, and electrophoretic pattern.—No effect which could reasonably be attributed to methandienone was observed upon these values.

Particular attention was paid to any changes in the serum-albumin that might arise with methandienone therapy. Useful studies were only possible in twenty-five patients. In seven (cases 1, 3, 8, 11, 17, 18, and 21) the serum-albumin was raised by 0·3 g. per 100 ml. or more. In thirteen (cases 2, 5, 6, 12–15, 22–24, and 28–30) the serum-albumin did not change significantly, taking this to mean no change greater than ±0·3 g. per 100 ml. In five patients (cases 7, 9, 10, 16, and 19) the serum-albumin fell with methandienone by more than 0·3 g. per 100 ml. In three of these (cases 9, 10, and 16) the fall could reasonably be attributed to the disease process, case 9 having chronic pyelonephritis with albuminuria, case 10 postgastrectomy steatorrhœa, and case 16 Cushing's syndrome. In case 7 the serum-albumin fell from 4·4 to 3·7 g. per 100 ml., and in case 19 from 3·9 to 3·4 g. per 100 ml.



The results of S.G.O.T. estimations in all the patients showing increases above 40 units per ml. while taking methandienone for less than 70 days (a) and more than 70 days (b).

TABLE II—S.G.O.T. LEVELS IN TWO GROUPS OF PATIENTS TAKING METHANDIENONE 50–100 mg. OR 5–25 mg. DAILY.

—	Pre-treatment S.G.O.T.	Days of methandienone therapy							
		1–7	8–14	15–28	29–42	43–70	71–98	99–126	127–154
Mean in 13 patients given 50–100 mg. daily	18 units per ml.	53	89	64	37	25	30	38	34
Mean in 13 patients given 5-25 mg. daily	22 units per ml.	18	22	36	21	41	28	16	20

Urinary bilirubin, urobilinogen, and aminoacid excretion.—No patients showed increase in excretion of urinary bilirubin, urobilinogen, or aminoacids while taking methandienone.

S.G.O.T.—The effect of methandienone on the S.G.O.T. was studied in thirty patients, and in three of them two separate courses of the drug were given. The S.G.O.T. was raised above the upper limit of normal (40 units per ml.) in 10 studies (30%) of eight patients. In a further five patients having methandienone (cases 14, 19, 21, 24, and 28) the S.G.O.T. became transiently raised by more than 10 units per ml. as compared with the pre-treatment level. In these five cases, however, the increase was never above 40 units per ml., and we did not regard this as definitely abnormal.

The results of the 10 studies in which the S.G.O.T. rose above 40 units per ml. are shown in the figure. The patients were arbitrarily grouped into short-term (a) and long-term (b) studies, depending upon whether they had had methandienone for more or less than 70 days.

The abnormal increase of S.G.O.T., the levels of which ranged from 41 to 280 units per ml., usually arose early in the course of methandienone treatment, reaching a peak in about 3 weeks. In three patients (cases 7, 10B, and 11) a single transitory mild increase of S.G.O.T. was found later (at 95, 161, and 44 days respectively).

In the five studies shown in figure (*a*) the drug was stopped when the S.G.O.T. level was increased. In case 16 the S.G.O.T. was not estimated later. In the other four studies, however, the levels returned to normal in 4–16 days.

In the five cases shown in figure (*b*) the S.G.O.T. fell to below 40 units per ml. from its peak in less than 40 days, despite continued administration of the drug.

In study 5B (figure [*a*]) there was an unusually early (7 days) and large rise of S.G.O.T. (to 240 units per ml.) which we are unable to explain. 2 months before her second course of methandienone, the patient had undergone hypophysectomy for Cushing's syndrome, with only partial relief. Since this study she has taken methandienone 15 mg. daily for 90 days with considerable clinical benefit, but without evidence of liver dysfunction.

We found no relation between increase of S.G.O.T. during methandienone treatment and the sex and age of the patient. The S.G.O.T. was more often raised in patients receiving higher doses of methandienone, as can be seen from table II. This compares two groups of thirteen patients, one of which received methandienone 50–100 mg. daily, and the other 25 mg. or less. In about a third of the patients given methandienone the S.G.O.T. showed an increase to less than 300 units per ml. The increased levels returned to normal whether or not the drug was continued.

45-minute % retention of B.S.P.—For convenience we have again divided the patients into groups studied for less than 70 days or more than 70 days:

Short-term studies were made on nineteen patients, and the results are summarised in table III. Where the B.S.P. retention was estimated more than once in any single week, the results

TABLE III—SHORT-TERM STUDIES OF B.S.P. RETENTION

Case no.	Dose of methandienone (mg. per day)	% B.S.P. retention before methandienone	Days of methandienone therapy						Days after discontinuing methandienone		
			1–7	8–14	15–21	22–28	29–35	36–70	1–7	8–14	15–21
1(A)	50	12·5	..	..	..	26·0	17·5	..	..	14·1	11·3
5(B)	50	3·0	15·2	23·0	..	..	..	..	13·1	5·1	..
10(A)	25	3·0	..	3·6	3·6	..	4·4	..	..	..	..
11	25–50	4·2	10·8	..	..	19·0	22·0	24·0	29·5	19·0	10·8
12	50	1·0	1·0	4·6	..	..	..	..	..	..	..
13	25	3·0	2·1	..	3·5	..	..	..	..	..	..
14	50	1·4	6·0	..	1·7	..	..	..	1·4	..	..
15	25	9·9	..	29·0	..	..	..	..	10·1	..	..
16	50	..	11·0	..	9·8	..	..	..	..	..	..
18	50	6·2	5·4	6·0	..	..	..	..	6·1	..	..
19	50	2·4	..	..	14·1	..	..	11·8	4·0	..	..
20	50–100	..	..	..	6·0	..	..	..	..	..	..
21	50	1·5	..	..	23·5	..	..	..	5·1	..	..
22	25	3·0	..	10·0	..	..	..	..	..	6·1	4·0
24	100	7·5	12·6	19·5	19·7	16·6	..	..	9·7	..	3·2
28	10–20	2·4	5·0	..	9·9	..	..	7·0	2·1	..	..
29	20	4·7	..	5·7	7·5	..	..	..	..	..	..
30	5–20	1·0	..	..	5·0	10·0	..	..	21·	..	..
33	25	11·1	..	4·0	..	..	1·0	2·0	..	..	..

were averaged. The B.S.P. retention rose above 6% in twelve (62%) of these nineteen patients. In nine patients (cases 1A, 5B, 15, 19, 21, 22, 24, 28, and 30) the increased B.S.P. retention returned to normal or to the pretreatment level within 3–19 days of stopping the drug, and it was already starting to fall before this in cases 1A, 19, 24, and 28. Of the remaining three patients whose B.S.P. retention became abnormal with methandienone therapy, further estimations were not made in two (cases 16 and 29) after the drug was stopped. Case 11 showed B.S.P. retention as early as 4 days after starting methandienone, and the B.S.P. retention continued to rise until it was 24% at 44 days. The drug was then discontinued, but the later course was complicated by a severe allergic reaction, probably due to furadantin prescribed to treat her severe chronic pyelonephritis. 23 days after stopping methandienone, at the time of discharge, her B.S.P. retention was still 11%, and this patient showed the slowest recovery of B.S.P. function of all our patients. It is perhaps relevant that her creatinine-clearance was only 20 ml. per min. The effect of impaired renal function on the hepatic effects of anabolic steroids will be further investigated.

Long-term studies in fourteen patients are summarised in table IV. Eleven patients (80%) (cases 1B, 2–4, 5A, 6, 7, 10B, 17, 23, and 31) showed an elevation of B.S.P. retention above 6%. In cases 8, 9, and 32 the B.S.P. retention was not significantly increased. These findings suggest a delay in B.S.P. excretion in most patients receiving methandienone. It can also be seen that the B.S.P. excretion tends to return to normal values or pretreatment levels when methandienone therapy is continued at the same dosage. Thus in six patients (cases 1B, 2, 3, 10B, 17, and 23) B.S.P. retention had returned to below 6% or to the pretreatment level while methandienone therapy was continued, the time taken being 70–126 days. In four of the remaining five patients with abnormal B.S.P. retention (cases 4, 5A, 6, and 31) the B.S.P. fell towards normal but is still slightly increased.

One patient (case 7) is of special interest because on only methandienone 20 mg. daily the B.S.P. retention continued to rise, reaching 31% at 95 days; it was still 20% after 259 days of therapy. In this patient other liver-function tests were normal except for a transient rise of serum-bilirubin to 2 mg. per 100 ml. (at 57 days), and of S.G.O.T. to 62 units per ml. (at 95 days).

In considering both the short-term and long-term studies, B.S.P. retention increased abnormally in twenty-three patients (70%). This inability to deal normally with B.S.P. arose early during methandienone administration, often within the first fortnight, and always within 3 months. The greatest increase of B.S.P. retention in our study was 34% (case 2) and only one other patient showed an increase above 30% (case 7). No clear correlation was found between the dose of methandienone and the frequency or extent of abnormal B.S.P. retention (e.g., cases 1A, 1B, 7, and 11).

Effects of Methandienone in Patients with Pre-existing Liver Disorder

Seven patients had liver disease or abnormal liver-function tests before starting methandienone. The details are:

Case 1, with acute intermittent porphyria and postmenopausal osteoporosis, had an abnormal B.S.P. retention of 12·5% before treatment with methandienone.

Case 2, a young man with acute idiopathic osteoporosis, had a serum-bilirubin of 1·3 mg. per 100 ml. and an abnormal B.S.P. retention of 15% before treatment.

Case 13 had toxic jaundice 14 days before methandienone therapy. At this time her serum-bilirubin was 11 mg. per 100 ml. and she had an abnormal B.S.P. retention of 27%. The day before treatment with methandienone the bilirubin level and B.S.P. tests were normal.

Case 15 had carcinomatosis, with liver secondaries, from carcinoma of breast.

Case 16 proved at necropsy to have multiple liver secondaries from an adrenal carcinoma.

Case 26, a woman with anorexia nervosa, had an abnormal B.S.P. retention (13%), and increased serum-bilirubin (1·6 mg.

TABLE IV—LONG-TERM STUDIES OF B.S.P. RETENTION

Case no.	Dose of methandienone (mg. per day)	% B.S.P. retention before methandienone	Days of methandienone therapy									
			1–14	15–28	29–42	43–70	71–98	99–126	127–154	155–182	183–210	211–260
1(B)	25	11·3	..	20·8	21·2	..	23·0	9·7	10·1	10·1	..	..
2	75–100	15·0	..	19·5	34·0	22·5	20·0	19·5	16·8	15·7	..	..
3	25	4·0	..	5·2	11·2	22·2	6·0	..	..	..	..	..
4	25	3·5	..	..	12·0	11·5	10·0	..	..	..	..	..
5(A)	12·5–100	7·4	..	..	28·0	21·1	15·6	18·1	15·2	..	10·1	..
6	12·5–50	4·0	..	17·2	7·1	10·2	..	9·2	7·1	7·0	..	..
7	20	1·6	..	1·0	..	9·4	31·0	..	25·5	..	24·7	20·1
8	50	1·0	1·0	1·0	1·1	1·0	..	..	..	..	..	..
9	25	..	..	..	..	3·2	1·8	4·3	4·2	1·0	3·0	2·6
10(C)	25	3·0	..	..	7·4	..	3·6	..	1·7	3·1	4·1	..
17	25–50	2·5	2·3	5·5	6·0	10·1	6·0	4·8	..	..	..	..
23	50	1·1	..	..	7·8	..	2·6	2·6	..	..	..	..
31	25–50	..	..	..	..	..	17·1	7·1	..	..	..	..
32	25	..	..	1·2	1·3	2·5	2·1	..	..	..	..	..

TABLE V—STUDIES OF THE EFFECT OF ANABOLIC STEROIDS ON B.S.P. EXCRETION AND S.G.O.T. LEVELS

Report	No. of subjects	Subjects	Liver function before methandienone	Drug given	Dose of drug (mg. per day)	Length of administration	% showing 45-minute retention of B.S.P. above 6%	% showing elevation of S.G.O.T.
Carbone et al. (1959) ..	17	Patients	Normal	Methyltestosterone	67	3 wks.	90	40
Heaney and Whedon (1958)	5	„	„	„	100	Not given	100	..
	11	7 patients and 4 healthy controls	„	Norethandrolone	20–100	„ „	100	..
Dowben (1958)	6	Healthy laboratory workers	„	„	30	6 wks.	100	100
Kory et al. (1959).. ..	47	Patients	„	„	25 or 50	6 mos.	72	..
	10	„	„	„	25	5 wks.	90	70
					50	3 wks.		
Schaffner et al. (1959) ..	27	Chronically ill elderly patients	„	„	60	3–5 wks.	..	60
Present study	19	See table I	Normal in 23, abnormal in 7	Methandienone	10–100	Less than 70 days	62	20
	14			„	10–100	More than 70 days	80	45

per 100 ml.) and alkaline phosphatase (12 King-Armstrong units), 18 days before starting methandienone. On a high-protein/high-calorie diet, these parameters of liver function fell to normal by the day immediately before the drug was given.

Case 33, a man with asthma and chronic bronchitis who was admitted to hospital with gross osteoporosis and vertebral and rib fractures, due to prolonged corticoid therapy, had an abnormal B.S.P. retention of 11%.

We were not able to discern any increased susceptibility to changes either in the B.S.P. test, S.G.O.T. levels, or any other liver-function tests while these patients were given methandienone, compared with the rest of the patients studied.

Discussion

The results of our studies of hepatic function in thirty patients receiving methandienone have shown no liver disorder recognisable by clinical signs or symptoms, while most of the liver-function tests employed were undisturbed. Two tests, however, showed changes—namely, the S.G.O.T. and the B.S.P. retention.

Testosterone and its esters—e.g., testosterone phenylpropionate or the related compound norandrolone—are not thought to cause liver disturbance, but they must be given sublingually or by injection, which is inconvenient. The substitution of an alkyl group in the 17α position in the steroid nucleus results in compounds which are active when given by mouth, but this group of compounds have been responsible for liver toxicity. Apparently it is not the oral route, producing high portal blood-levels, which causes them to have hepatotoxic effects, since the same compounds given parenterally also alter liver function (Foss and Simpson 1959).

Although several C17-alkyl substituted derivatives of testosterone are potentially hepatotoxic, clinical evidence of this toxicity is rare. Foss and Simpson (1959), reviewing the work on jaundice attributed to the use of methyltestosterone, were only able to find forty-two cases. Only one death has been recorded (Koszalka 1957). This is a reasonable record of safety, considering the widespread use of methyltestosterone during the past 20 years, often for patients who were seriously ill—e.g., with disseminated carcinoma of the breast.

Norethandrolone (17α-ethyl-19-nortestosterone), one of the most widely used of the new synthetic anabolic steroids, has been available for less than 5 years. Already some reports have appeared of jaundice attributed to the use of the drug (Dunning 1958, Schaffner et al. 1959, Foss and Simpson 1959, Melrose 1960, Gordon et al. 1960). Two out of ten patients given 17α-methyl-19-nortestosterone showed elevation of serum-bilirubin (Peters et al. 1958), which brings into question the safety of this compound. Jaundice has been reported in a patient receiving one of the new ovulation inhibitors—namely, norethisterone (17α-ethynyl-19-nortestosterone, 'Norlutin') (Tyler and Olson 1959).

The pattern of jaundice, when it appears, is essentially the same for all these drugs, usually following some months' administration, though occasionally arising after only 1 or 2 weeks. The patient complains of anorexia, nausea, listlessness, and lethargy, followed in a few days by obstructive jaundice with pale stools and excess bile in the urine. Together with bilirubinæmia there is slight or moderate increase of serum-alkaline-phosphatase activity and increase of S.G.O.T. to levels less than 500 units per ml. When the drug is discontinued jaundice settles within days or months, and usually does not recur if the drug is given again later (Werner et al. 1950).

The histology of the liver at the time of jaundice, either due to methyltestosterone or norethandrolone is the same—namely, that of cholestasis.

Cholestasis has been defined as a phenomenon produced by interference with bile-flow after its formation by the liver cells (Popper and Schaffner 1957). Histologically it comprises dilatation of the intralobular bile canaliculi, many of which are plugged with bile thrombi, and there may be excess bile pigment in the hepatic parenchymal and Kupffer cells. The main bile ducts are not dilated, and contain no bile. Cholestasis is also characterised by the absence of recognisable hepatocellular damage or of inflammatory cell accummulations in the portal zones.

The cause of cholestasis is not understood, but it may be due to an increase in the viscosity of the bile, brought about in some way by these steroids (Schaffner et al. 1959). Gutman (1957) lists several other drugs used in treatment which cause cholestasis.

We would again emphasise that jaundice is a rare complication of therapy with the anabolic steroids, and most patients given these drugs show no signs or symptoms of hepatic toxicity, the serum-bilirubin, alkaline phosphatase, thymol-turbidity, thymol-flocculation, and plasma-protein levels remaining normal. But in the few studies where these estimations have been made, many of these patients have shown an increase of S.G.O.T., and there has been an increased retention of B.S.P., with more than 6% of the dye remaining in the plasma 45 minutes after its injection.

Table V summarises previous reports of the effect of methyl testosterone and norethandrolone on B.S.P. retention and S.G.O.T. levels, and shows the frequency with which such tests become abnormal in patients taking these drugs. With one exception these studies lasted only a few weeks. But the long-term effects of these steroids are more important. There is only one previous report of such a study. Kory et al. (1959) gave forty-seven patients

25–50 mg. daily of norethandrolone for 6 months. Thirty-five patients (74%) showed increased B.S.P. retention, this effect being greater when 50 mg. of the drug was given rather than 25 mg. The highest B.S.P. retention in this study was 57%.

When the B.S.P. retention and S.G.O.T. are increased liver biopsy may be normal. Kory et al. (1959) found no evidence of cholestasis in liver biopsies in seven of their patients given norethandrolone when their B.S.P. retention was increased. Similarly Schaffner et al. (1959), by needle biopsy, at the end of a 3–5 week course of norethandrolone (60 mg. daily), found evidence of cholestasis in only four of twenty-seven patients, although 60% of them had had increased S.G.O.T. at some time during therapy. They did find S.G.O.T. levels above 180 units per ml., however, in the four patients with cholestasis, and these four showed a greater increase of S.G.O.T. than did the patients without cholestasis.

In our study, the effects of methandienone on liver function seemed to follow the pattern found with the other anabolic steroids. We encountered no clinical evidence of hepatic toxicity, even after long-continued administration of methandienone in very high doses, and in patients with pre-existing liver dysfunction. The classical liver-function tests (serum-bilirubin, alkaline phosphatase, thymol-turbidity, thymol-flocculation, total proteins, A/G ratio, serum electrophoresis, and urinary bilirubin and urobilinogen) have all failed to reveal significant changes which might be due to hepatic toxicity. As with methyltestosterone and norethandrolone, however, methandienone increases the S.G.O.T. and B.S.P retention in many cases.

About 70% of our patients receiving methandienone showed, at some stage, increased B.S.P. retention. The highest value was 34%. We have already referred to the fact that B.S.P. retention tends to return to pretreatment levels whether or not methandienone is continued, but one patient (case 7) is an apparent exception.

The metabolism of B.S.P. involves the following processes:

After intravenous injection, B.S.P. is bound to the serum-albumin, is taken up by the liver cells where it is stored, and is then conjugated with cysteine, and possibly also with glutathione, to form a mercaptide (Grodsky et al. 1959). Finally it is secreted into the bile.

Chromatographic analysis of B.S.P. metabolites in the blood of patients taking methyltestosterone showed that about 40% of the retained B.S.P. was in the conjugated form—a proportion similar to that found in patients with extrahepatic obstruction. In patients with viral hepatitis or cirrhosis the proportion of retained B.S.P. in the conjugated form was much less, namely 8 and 17% respectively (Carbone et al. 1959). Our findings with methandienone are similar to those mentioned above for methyltestosterone.

Carbone et al. (1959) suggest that B.S.P. retention in patients given methyltestosterone may be due to a "metabolic block" in the excretory mechanism, so that the conjugated B.S.P. fails to enter the bile and is reabsorbed from the hepatic cells. Their suggestion is based upon the fact that B.S.P. retention can be extremely high without increase of serum-bilirubin or alkaline phosphatase—changes which would be expected if there were physical obstruction.

Perhaps too much emphasis should not be laid upon the B.S.P. test as a measure of hepatic function in patients receiving anabolic steroids, since the degree of retention which can be demonstrated is out of proportion to changes in other parameters of liver function. Not to take this view would preclude the clinical use of steroids such as methyltestosterone, which can be shown to increase the B.S.P. retention in most patients.

We have found an increase of S.G.O.T. in about a third of our patients, and our study suggests that increase of the S.G.O.T. is more likely if the dose of methandienone is 50 mg. daily or more. The S.G.O.T. usually increases early in the course of treatment, although in three patients the increase was late, transient, and mild. If increased when methandienone is discontinued the S.G.O.T. rapidly falls to normal, and even when the drug is continued the levels return to normal, though rather more slowly. Our patients showed no correlation between the increase of S.G.O.T. and the level of B.S.P. retention, but with two exceptions (cases 3 and 10B) the S.G.O.T. was not increased unless the B.S.P. retention was also raised.

Sachs and Lanchentin (1960), in their work on S.G.O.T. levels associated with liver disease, found very high levels characteristically in excess of 500 units per ml., when hepatocellular destruction was present. When jaundice was obstructive in type, either extrahepatic or intrahepatic, the S.G.O.T. was lower, not exceeding 500 units per ml.

In our study the range of increase of S.G.O.T. was 41–280 units per ml., which indicates an obstructive rather than an hepatocellular destructive lesion. Such an interpretation would fit the cholestasis found by needle biopsy in some patients taking methyltestosterone or norethandrolone. Often, however, the S.G.O.T. is increased when the liver biopsy is apparently normal. While interference with the flow of bile is a possible explanation of increased S.G.O.T. in patients having anabolic steroids, other explanations are possible. Dowben (1958) found not only an increase of S.G.O.T. in all six laboratory workers to whom he gave norethandrolone 30 mg. daily for 6 weeks but also increase of the serum-lactic-dehydrogenase and serum-aldolase. As aldolase is primarily found in muscle, he speculated that the enzyme increases in patients treated with norethandrolone were more likely to be due to a direct cellular effect than to secondary hepatocellular involvement as a consequence of biliary obstruction.

Conclusions

Earlier work and our studies suggest that patients receiving any of the C17α-alkyl-substituted testosterone derivatives may show hepatic effects, which fall into the following categories:

1. Most patients have no clinical or histological evidence of hepatic disorder. The classical liver-function tests are normal, but most cases show abnormal B.S.P. retention, and many have increased S.G.O.T. levels. Our results with methandienone suggest that these changes may be only temporary, even if the drug is continued at the same dose.

2. A few patients differ from the previous group in having, in addition to abnormal B.S.P. retention, a greater increase of S.G.O.T. (although less than 500 units per ml.). These would probably show histological evidence of cholestasis.

3. A very few patients, in addition to the findings in the second category, also have obstructive jaundice with a slight or moderate elevation of the alkaline phosphatase.

We do not consider that increased B.S.P. retention during administration of an anabolic steroid such as methandienone warrants stopping the drug, provided there are clinical indications for its use. We base this upon the facts that the full significance of the B.S.P. test is not known; that, at any rate with methandienone, the liver usually recovers its ability to excrete B.S.P. although

the drug is continued; and, most important of all, that many thousands of patients have had anabolic steroids for long periods, presumably with increased B.S.P. retention, while cases of jaundice are rare.

In our patients, S.G.O.T. increases were only temporary, and less than 300 units per ml. But it would probably be a wise precaution to stop these drugs if the S.G.O.T. increase persisted, or exceeded 300 units per ml., since other workers have found evidence of cholestasis, or jaundice, in such patients.

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OBSTETRIC ANALGESIA WITH PETHIDINE AND SCOPOLAMINE

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THE better care of the pregnant woman, the woman in labour, and the newborn infant contribute to the low maternal and perinatal mortality in Sweden today. Less has been done, however, to relieve the pain of the parturient woman, in spite of the fact that almost all deliveries now take place in hospital. The expectant woman is prepared psychologically at routine medical examinations in the antepartum period, by exercises, and by instruction in relaxation. In the delivery room, inhalational analgesics (nitrous oxide and trichloroethylene) are provided, but neither general anæsthesia nor local analgesia is given for a "normal" labour and delivery. The main arguments against a wider use of modern anæsthetic techniques in labour are that anæsthesia involves the risk of increasing maternal and perinatal mortality, and that Sweden is short of trained anæsthetists.

The purpose of our investigation was to study the parturient woman's evaluation of the pain experienced during labour, and to assess to what extent this pain will fall into oblivion. Furthermore, we thought it interesting to show the effect of an analgesic (pethidine) and an amnestic (scopolamine) on the evaluation of pain during and after labour, and to determine the dosages necessary to secure a good relief of pain (at least retrospectively), without involving the risk of undue complications.

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Methods

Most parturient women were prepared ante partum by a technique similar to that of Dick Read. When labour began, they were brought to the delivery room. Nitrous oxide and trichloroethylene were available, but the choice was left to the woman. (Pure nitrous oxide was delivered intermittently, 2 to 5 litres at a time, from an 'Aga-Sedator' [Kinch 1952]. Trichloroethylene vapour was administered in air at a maximum concentration of 0·5%.) A record was kept of the inhalational agent or agents used during the first stage of labour. No general anæsthesia was given at the time of delivery.

845 healthy parturient women with a "normal" presentation at term were divided in two groups:

Group I

This consisted of women in labour brought to the delivery rooms between the twentieth and the last day of each month, and was taken as a control series. No intramuscular injections were given during labour.

Group II

During the first stage of labour, all women in this group were given intramuscular injections from coded ampoules. At onset of labour, the mother received an initial injection of 2 ml., and then of 1 ml. every three to four hours, as needed, until onset of the second stage of labour. Women brought to the delivery rooms the first to nineteenth day of each month were selected for this group.

The contents of the ampoules, which were not known to the mothers or to the investigators, were:

A. Placebo. 0·9% saline solution.
B. Pethidine-scopolamine. 50 mg. pethidine and 0·2 mg. scopolamine per ml.
C. Pethidine. 50 mg. per ml.
D. Scopolamine. 0·2 mg. per ml.

Pain experienced during labour was evaluated during actual labour, on the first day after delivery, and when the mother left hospital—i.e., the fourth to fifth postpartum day. During labour, the women were repeatedly asked by the midwives to estimate the degree of pain felt. In the postpartum period, they were interviewed by the doctor in charge of the postpartum ward. The midwives also tried to assess objectively the pain felt by the mothers during labour. The severity of pain was rated as: (1) none or slight, (2) moderate, or (3) severe.

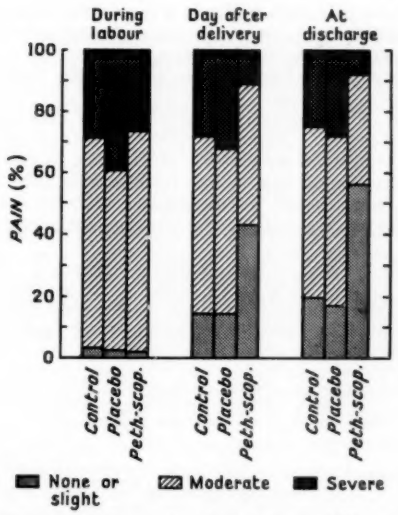

Fig. 1—The results of assessing showed that pethidine-scopolamine injected intramuscularly during the first stage of labour enhanced the normal tendency to forget the pain experienced during labour. (Peth.-scop. = pethidine-scopolamine.)

TABLE I—THE ASSESSMENT OF PAIN

Series	Number of cases	Pain as assessed: During labour — By the mother: None or slight (%)	By the mother: Moderate (%)	By the mother: Severe (%)	By the midwife: None or slight (%)	By the midwife: Moderate (%)	By the midwife: Severe (%)	The day after delivery by the mother: None or slight (%)	The day after delivery by the mother: Moderate (%)	The day after delivery by the mother: Severe (%)	At discharge, by the mother: None or slight (%)	At discharge, by the mother: Moderate (%)	At discharge, by the mother: Severe (%)
I. Control	247	3	69	28	7	84	9	14	58	28	20	55	25
Primiparæ	99	1	67	32	3	83	14	13	67	20	20	58	22
Multiparæ	148	4	70	26	10	85	5	15	52	33	20	54	26
IIA. Placebo	243	2	59	39	3	89	8	14	54	32	17	55	28
Primiparæ	118	2	58	40	2	89	9	12	54	34	13	58	29
Multiparæ	125	2	61	37	5	88	7	15	54	31	21	52	27
IIB. Pethidine-scopolamine	236	2	72	26	5	88	7	43	46	11	56	36	8
Primiparæ	129	2	71	27	7	85	8	37	47	16	53	38	9
Multiparæ	107	4	72	24	4	90	6	50	44	6	60	32	8
IIC. Pethidine	67	0	52	48	..	..	..	14	54	32	18	54	28
IID. Scopolamine	53	3	61	36	..	..	..	21	46	33	28	41	31

The condition of the newborn infant was evaluated according to the method of scoring described by Apgar (1953). Sixty seconds after the delivery, heart-rate, respiration, reflex activity, colour of the skin, and muscle-tone were ascertained by a midwife. Each sign was given a score of 0, 1, or 2—the highest possible total score of 10 indicating the best possible condition of the newborn infant. Complications encountered during labour, which might affect the infant, resulted in its exclusion from this study, irrespective of the rated score. Infants with congenital anomalies were also excluded.

In addition, duration of labour and the occurrence of excessive postpartum bleeding (i.e., 500 ml. or more) were recorded.

TABLE II—INHALATIONAL ANALGESIA USED BY MOTHER

Series	Percentage of mothers using inhalational analgesia during first stage
I. Control	56
IIA. Placebo	48
IIB. Pethidine-scopolamine	34

Results

The results of the assessment of pain are shown in table I and in fig. 1. The extent to which inhalational analgesics were used is recorded in table II.

Group I (Control) and Group IIA (Placebo)

Good agreement was found between control and placebo groups particularly in the postpartum evaluation of the pain.

The degrees of pain during labour, as assessed by the midwives, varied little, but differed considerably from those reported by the mothers.

In spite of the antepartum care and the availability of inhalational analgesics, about 30% of the mothers during labour described the pain as severe; 70% of them as moderate.

The interviews during labour revealed that 20% of the parturient women were placebo-reactors (53/253)—i.e., they said that the pain was less after the injection of the placebo than before.

When questioned in the postpartum period, the women described the pain experienced during labour as being somewhat less than they had said before; and, on discharge from hospital, 20% said the labour pain had been slight or non-existent.

TABLE III—DURATION OF LABOUR, FREQUENCY OF UTERINE INERTIA, AND FREQUENCY OF POSTPARTUM HÆMORRHAGE

Series	Average length of labour in primiparæ (hours)	Hypotonic inertia	Postpartum hæmorrhage of 500 ml. or more
I Control	$14^{3}/_{7}$	14/247 (6%)	69/247 (28%)
IIA. Placebo	$15^{1}/_{8}$	10/243 (4%)	86/243 (35%)
IIB. Pethidine-scopolamine	$16^{3}/_{10}$	22/236 (9%)	43/232 (19%)

Primiparæ did not differ from multiparæ in their estimation of labour pain.

Group IIB (pethidine-scopolamine), C (pethidine), and D (scopolamine)

During labour, the pain described was about the same as in the two groups I and IIA. Inhalational analgesia, however, was used less in the pethidine-scopolamine groups than in the control and placebo groups (table II).

In the pethidine-scopolamine groups, many of the women could not, postpartum, recollect the pain felt during labour, so that on discharge from the hospital less than 10% of the women described the labour pain as severe, and 55% said they had had slight pain or none at all.

Group IIC (pethidine) and D (scopolamine) are considered as pilot groups. They indicated that pethidine alone or scopolamine alone did not much enhance the normal tendency to forget the labour pain, and the groups were, therefore, not completed. The results of preliminary control groups (placebo and pethidine-scopolamine) comprising 50–70 mothers did not differ from those of the complete series.

The incidence of mothers who became excited and uncooperative was low in the pethidine-scopolamine groups (8/236). Half of these received more than two injections—i.e., more than 0·6 mg. of scopolamine. A few mothers in the placebo group were excited and uncooperative (3/242).

TABLE IV—INFANT-SCORES

Series	Total score 10–8	Total score 7–5	Total score 4–0	Mean of total scores
I. Control	237/245 (97%)	9/245	0	9·6
IIA. Placebo	229/241 (95%)	12/241	0	9·6
IIB. Pethidine-scopolamine	207/232 (89%)	19/232	6/232	9·0

Unsatisfactory skin colour and muscle tone were responsible in most cases for a low total score. Resuscitation measures were undertaken in 5/232 infants in the pethidine-scopolamine series.

The duration of the labour was about the same in the three main groups (table III). Hypotonic inertia, however, during labour was found more often in the pethidine-scopolamine group than in the others. Postpartum bleeding, found more frequently in the control and placebo groups, seems to be related to a more extensive use of trichlorethylene.

Infants of mothers included in control and placebo groups were considered to be born in a good condition—95% of them had a score of at least 8. The results of these two groups were identical (table IV). In the pethidine-scopolamine groups (IIB,) less than 90% of the infants were regarded as being in a good condition (total score 8 or more), and some were born in a fairly poor condition (total score less than 5, table IV). The present findings also suggest that repeated injections of pethidine-scopolamine and the use of trichloroethylene during first and second stage of labour were followed by a lowered total score (tables V and VI). The distribution of time from last injection to birth was, however, the same in those deliveries

TABLE V—NUMBER OF INJECTIONS IN THE PETHIDINE-SCOPOLAMINE SERIES

Number of injections	Whole series	Infant score (total)	
		10–8	7–0
1	166/232 (71%)	153/166	10/166 (8%)
2	55/232 (24%)	47/55	5/55 (15%)
3 or more	11/232 (5%)	7/11	4/11 (36%)

giving birth to infants with a high total score as those with scores of 7 or less (fig. 2). No neonatal deaths occurred.

Discussion

Our results revealed a similarity between control and placebo groups, especially post partum, indicating the reliability of the method used. The present findings also show clearly that pain is a subjective sensation which only can be assessed by the individual actually experiencing it. Evaluations of pain by the midwives were generally similar, and differed from those made by the mothers.

In spite of the antepartum preparation and the availability of inhalational analgesics during labour, 30% of the mothers in the control and placebo groups complained of severe pain during labour, and only an insignificant number felt slight or no pain. The administration of pethidine during the first stage of labour did not appreciably affect the mothers' evaluation of the severity of the pain, though some relief was admitted. The use of inhalational analgesics was also less in the groups where pethidine was given than in the control and placebo series.

TABLE VI—INFANT SCORE (10–8) CORRELATED WITH THE INHALATIONAL AGENT USED BY THE MOTHER

Series	Nitrous oxide only	Trichloro-ethylene only	No inhalational analgesia
I. Control	59/62 (95%)	36/40 (90%)	105/108 (97%)
IIA. Placebo	58/60 (97%)	36/40 (90%)	120/126 (95%)
IIB. Pethidine-scopolamine	33/36 (91%)	30/38 (79%)	140/154 (91%)

The postpartum evaluation of pain showed that the pain experienced during labour is normally forgotten to some extent. This amnesia was greatly enhanced by the administration of pethidine-scopolamine during the first stage of labour. Pethidine alone, or scopolomine alone, was of little value. The present findings also suggest that scopolamine will only enhance amnesia when a certain minimum of pain relief is produced by pethidine (in some cases in combination with an inhalational agent), or when the pain experienced is considered to be slight or moderate (table I). The good results in the pethidine-scopolamine groups agree with those presented by Roberts (1948). Her results (82% good pain relief, 14% satisfactory, and 4 % fair from injections of pethidine-scopolamine during labour) were obtained by interviewing the mothers both during actual labour and on the first postpartum day. Her results probably correspond to those from the first postpartum interview in our study. The beneficial effect of pethidine-scopolamine seems to be that it helps the women to forget the pain experienced during labour. A small number of patients, however, are refractory to even large doses.

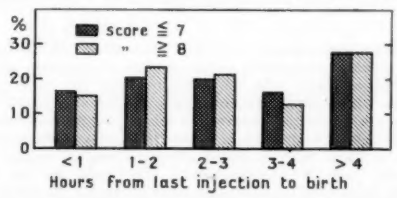

Fig. 2—The distribution of time from last injection to birth in the pethidine-scopolamine series was the same in those deliveries giving birth to infants with a high total score as in those with a low score.

In evaluating the effect of pethidine-scopolamine administered during the first stage of labour, the possible disadvantages of the drugs used have to be considered. Pethidine is known to affect the uterine tone during labour (Lindgren 1959). This drug is thus considered to be contraindicated in hypotonic inertia, but to be of value when uterine spasm, especially of the lower segment of the uterus and of cer ix, occurs. In this study, pethidine, given when labour was established, did not affect the duration of the labour or the amount of postpartum bleeding. The use of trichloroethylene during the first and second stages of labour seems, however, to carry the risk of a higher incidence of postpartum bleeding. The most probable explanation is that it depresses the tone of the uterine muscle, and that it is slowly eliminated after being given for a long period.

The use of scopolamine may cause the mothers to become excited and uncooperative. The frequency of this complication in the pethidine-scopolamine series was found to be about the same as in the placebo series, provided that the amount of scopolamine had not exceeded 0·6 mg.—(i.e., if not more than two injections were given).

The main disadvantage of pethidine and related drugs used in labour is their depressant effect on the infant. Pethidine has been found to depress the respiration of the newborn (Roberts et al. 1957), and to be followed by a lowered oxygen-tension in the arterial blood (Shields and Taylor 1957). In the present series, a slight difference was found between the total scores in the pethidine-scopolamine series and in the control and placebo groups. The similarity between the control and placebo groups, proving the reliability of the scoring test performed by a team of midwives, seems to indicate that the small difference between the control and placebo groups and the pethidine-scopolamine groups is a true difference, caused by the depressant effect of pethidine. The lowered vitality of the newborn in the pethidine-scopalamine series is not only correlated with the amount of pethidine given, but also with the amount of trichloroethylene inhaled, as the number of infants with a low total score was related to the administration of trichloroethylene during the first stage of labour. Interestingly enough, the time from the injection of pethidine to birth does not seem to influence the total score of the newborn infant (fig. 2). This agrees with Roberts' findings that pethidine injected more than four hours before birth caused as much respiratory depression as pethidine given later.

Summary

Pethidine-scopolamine injected intramuscularly during the first stage of uncomplicated labour at term, in combination with nitrous oxide, enhanced a normal tendency to forget the pain which had been felt thus rendering labour endurable in the postpartum recollection of the mother. The risk of unduly depressing the newborn infant, and of producing excitement in the mother seems to be negligible if the total dose of pethidine is kept below 150 mg., and that of scopolamine below 0·6 mg.—provided that trichloroethylene is not used for too long during labour.

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THE SINGLE-X NATURE OF SEX CHROMATIN IN MAN

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THE relative ease with which sex chromosome anomalies can now be found and classified depends largely upon the use of Barr's nuclear sexing technique in conjunction with refined cytological methods which permit accurate chromosome counts. The burgeoning number and variety of abnormalities makes imperative a precise definition of the relation between the sex chromatin and the sex chromosomes.

At one time, each sex-chromatin body was thought to represent fused heterochromatic regions of two X chromosomes, implying somatic pairing of the X pair in the cells of females. As the formation of interphase chromocentres was assumed to be a sine-qua-non of each heterochromatic region, the nucleus with one X should then contain a chromocentre half the size of the sex chromatin. The absence of such a chromocentre in the normal male nucleus was not explained.

Studies on germ and somatic cells of both sexes of rats have shown that sex chromosomes are composed almost entirely of heterochromatin, as indicated by characteristic condensation during specific stages of the cell life-cycle. At other stages, however, individual sex chromosomes do not thicken, but remain indistinguishable from the mostly euchromatic autosomes (Ohno et al. 1958, 1959, and 1960a). The behaviour pattern of individual sex chromosomes is shown in fig. 1. Since only one X chromosome in the female somatic cell displays precocious condensation, it became of considerable interest to determine whether in man, too, the sex chromatin represents a single X rather than fused heterochromatic regions of two Xs.

This report covers a series of studies, undertaken during the principal author's stay in Japan, on somatic cells of 13 fœtuses obtained after therapeutic abortions which are sanctioned by law in Japan.

Observations

After short-term tissue cultures, skin-cells and marrow-cells were examined employing hypotonic pretreatment squash technique. The cells were stained either with acetic-dahlia or by the Feulgen method. Feulgen-squash preparations were also made directly from liver and gonads of these fœtuses.

Although the cultures yielded a number of good prophase and metaphase figures, a nuclear sex difference at interphase was often obscured by the presence of obviously non-specific chromatin clumps. Thus, the positively heteropyknotic regions of prophase chromosomes could not be related with absolute certainty with the chromocentre of preceding interphase.

A truly reliable correlation between the morphology of interphase nuclei and individual chromosomes of subsequent prophase was possible with liver-parenchyma cells, because their large size permitted good spreading. Among the 13

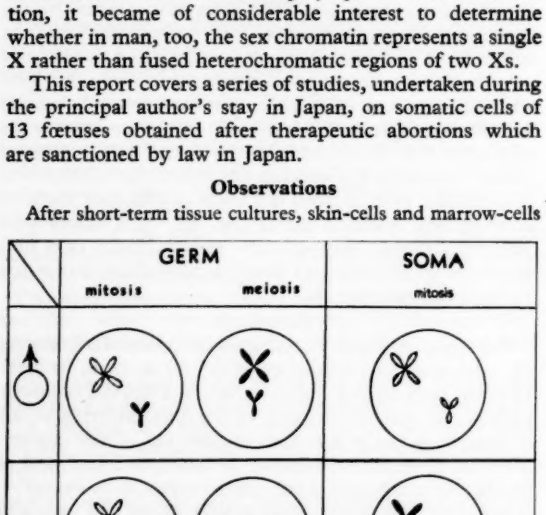

Fig. 1—Status of individual sex chromosomes in *Rattus norvegicus* is shown in germ and somatic cells of both sexes.

Heteropyknotic chromosomes are drawn solid black; chromosomes isopyknotic to the autosomes are outlined.

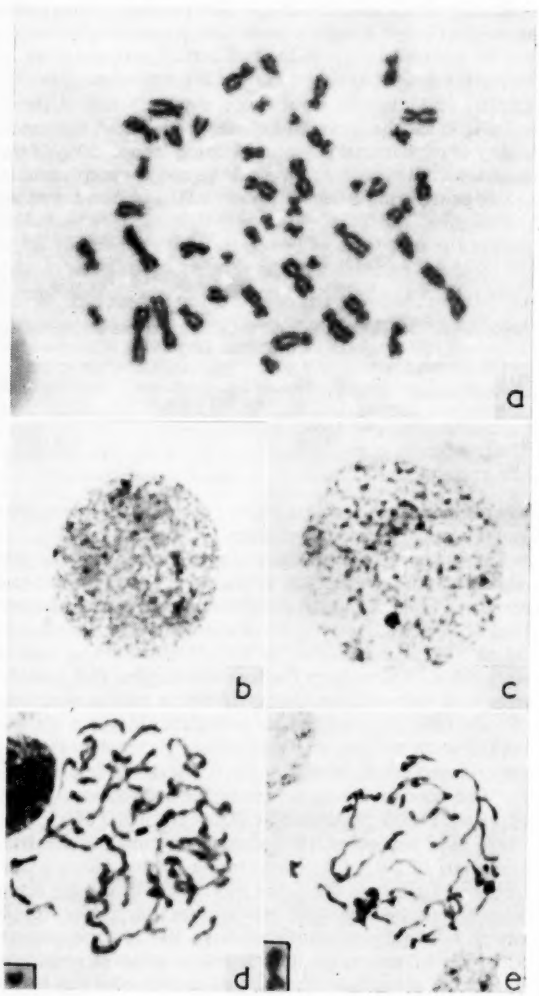

Fig. 2—Photomicrographs (×1200) of liver parenchymal cells from human fœtuses at about fourth month of gestation. (a) Female metaphase figure with 46 chromosomes; (b) male interphase nucleus with a small chromocentre, presumably representing the Y, discernible at top centre; (c) female interphase nucleus with sex-chromatin body plainly visible in lower centre; (d) male prophase nucleus with a small chromosome in centre distinctly showing positive heteropyknosis (the inset in the lower-left corner shows a small acrocentric metaphase chromosome presumed to be the Y); and (e) female prophase nucleus with one large chromosome at the lower left demonstrating precocious condensation (the inset in the lower-left corner shows the submediocentric metaphase chromosome presumed to be the X).

fœtuses studied, 2 at about the fourth month of gestation permitted determination of sex by gross anatomical examination. One was male and the other female; and, in each, the nuclear sex at interphase, and the chromosomal sex at metaphase, agreed with the anatomical findings. Figs. 2a – 2e are photomicrographs of liver-parenchyma cells obtained from these fœtuses. Fig. 2a illustrates an apparently normal female metaphase figure with 46 chromosomes. Figs. 2b and 2c show, respectively, male and female nuclei in interphase. Among several very small chromocentres always present in each male nucleus, one seemed more distinct than the others, as seen at the top centre of fig. 2b. Male nuclei were always void of a chromocentre approaching the size of the sex chromatin observed in female cells.

The female nucleus was characterised by the persistent presence of a sex-chromatin body (fig. 2c) which was by far the largest chromocentre found in either male or female nuclei.

At prophase of the male, provided only extremely flattened nuclei were dealt with, one very small chromosome, clearly demonstrating precocious condensation, could be seen in each nucleus. In size, this element closely resembled that of the five smallest acrocentric chromosomes in the male metaphase (fig. 2d). In the male diploid somatic cell, the Y but not the X appears to display precocious condensation and form the interphase chromocentre.

Only one chromosome in each female nucleus at prophase was heavily condensed along its entire length. This element—much larger than that seen in male nuclei—apparently represented a rather large chromosome. The mass corresponded roughly in size to that of the sex chromatin seen during interphase and that of the submediocentric chromosome belonging to the 6–12 group of female metaphase (fig. 2e). Thus, it appears likely that the sex chromatin of man, too, represents a single X chromosome.

Discussion

As early as 1956, cytological observations of certain human tumour cells led Atkin and Doxey (1956) to suspect the single-chromosome derivation of the sex chromatin. Circumstantial evidence supporting this is the finding that both XXX females (Jacobs et al. 1959 and 1960) and XXXY males (Barr 1960, Ferguson-Smith et al. 1960) apparently have two sex-chromatin bodies in many nuclei of their somatic cells. If two X chromosomes were needed to form a single sex-chromatin body, the cell with three Xs would be expected to contain only one sex-chromatin body.

As shown in fig. 1, the formation of an interphase chromocentre by one of the two Xs is characteristic of somatic cells but not oogonia and oocytes in rats. Both the two Xs of female germ-cells behaved in the same manner as the autosomes; therefore, they were sex-chromatin-negative. As will be reported in greater detail elsewhere, a similar situation is found in humans. Ovaries recovered from 2 stillborns in the seventh and ninth month of gestation revealed that oogonia are sex-chromatin-negative and the XX-bivalent of oocytes in the pachytene stage is indistinguishable from the autosomal bivalents.

Obviously, no individual X chromosome is inherently predetermined to manifest precocious condensation and form an interphase chromocentre. Why then does one of the two Xs in female somatic cells persistently form a sex-chromatin body?

At one time, paternal derivation was thought to be a factor. The situation now found in man, and previously found in opossums (Ohno et al. 1960b), favoured this idea, as one of the two Xs in the female as well as the Y of the male are paternally derived. When, however, the single paternally derived X in the somatic cells of X^pO female mice failed to display precocious condensation (Ohno et al. 1960c), this hypothesis was set aside.

The most convincing idea yet proposed appeared recently in a leading article in *The Lancet* (1960). This implies that one set of autosomes (2A) will suppress positive heteropyknosis in one X—for example, an XXX cell has one set of autosomes, one suppressor, and so two heteropyknotic Xs. However, Grumbach et al. (1960) report a case of chromatin-positive Turner's syndrome that is XO. If an XO cell can be sex-chromatin-positive, then yet another attractive hypothesis must be set aside while the task of finding one with a closer fit continues.

Summary

Studies on human fœtuses at about the fourth month of gestation show that the sex-chromatin body seen in female interphase nuclei represents a single X chromosome. These studies were suggested by earlier observations on rats, in which the single-X nature of sex chromatin was first described.

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SEX-CHROMATIN BODY IN NORMAL HUMAN TESTIS

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EARLY hypotheses about the nature of the sex-chromatin body must now be discarded (Barr 1959), and it has been suggested (Stewart 1960) that sex chromatin is derived from the heterochromatic segment of a single X chromosome. We present here further evidence in favour of this hypothesis. It is well known that the sex chromosomes exhibit allocycly in most animal species, and we have confirmed this in man. We wish, however, to draw attention to the presence in normal male germ-cells of a structure, apparently identical with the sex-chromatin body, although not previously correlated with it.

Materials and Methods

Normal human testicular tissue was obtained from biopsy or orchidectomy specimens in cases of torsion, suspected seminoma, herniorrhaphy, or carcinoma of prostate. The specimens were obtained from seven patients whose ages ranged from 17 to 75 years. The testicular tissue was examined in squash preparations, both fresh and fixed in alcohol-acetic, both with and without hypotonic and demecolcine pretreatment. The preparations were stained with aceto-orcein, lacto-aceto-orcein, or Feulgen. In each patient the nuclear sex was

determined from an oral mucosal smear or from somatic cell nuclei in a histological section of the testis.

Results

In all seven subjects the nuclear sex, by conventional methods, was clearly chromatin-negative. In testicular preparations from three of the seven subjects, suitable plates were obtained. The chromosome number (46) and the sex-chromosome constitution (XY) were confirmed from primary spermatocyte metaphases or from spermatogonial metaphases. These studies established that the subjects had a normal male karyotype yet in all seven there was sex chromatin present in about 10% of germ-cell nuclei.

In squash preparations, sex chromatin was seen in some nuclei of cells still within the seminiferous tubules (fig. 1), and was most clearly seen in the nuclei of primary

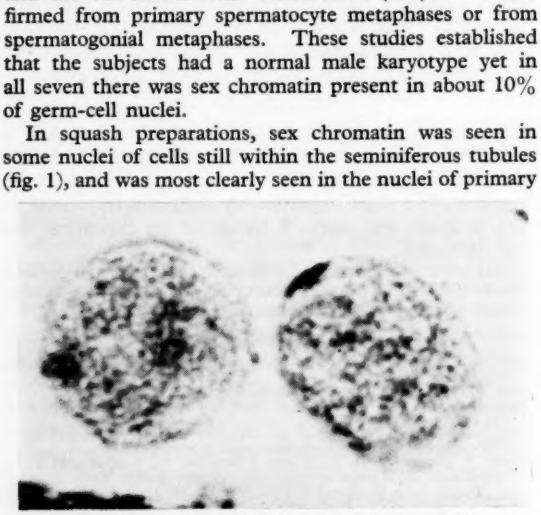

Fig. 1—Germ-cell nuclei within a seminiferous tubule.
The nucleus on the right, oval in shape, measuring 15 μ in greater diameter and with sex chromatin at 11 o'clock, is probably from a spermatogonium. ($\times$ 2000.)

spermatocytes which had been disgorged from the tubules (fig. 2). The sex-chromatin body was present in cell nuclei of different sizes, apparently in spermatogonia and in primary and secondary spermatocytes. It was most prominent in primary spermatocyte nuclei during very early prophase, and in some of these nuclei it appeared to be connected to the nucleolus by a fine chromatin thread. Primary spermatocyte nuclei were also seen with a second smaller structure at the nuclear membrane and with several structures in this position. During the later stages of early prophase the sex-chromatin body became larger and vesicular or elongated; and, in late prophase, a heteropyknotic condensation, apparently the X or XY chromosome complex, was present.

Discussion

Although much work remains to be done, these preliminary studies appear to support the view (Stewart 1960) that the sex-chromatin body is derived from the heterochromatic portion of a single X chromosome. They suggest that the heterochromatin of the single X chromosome of the male can be stained at the nuclear membrane during early prophase in the same way as the heterochromatin of superfluous X chromosomes during interphase. The occurrence of sex chromatin together with a smaller Feulgen-positive structure at the nuclear membrane in some nuclei, and of several such structures in others, suggests that the heterochromatin of the Y chromosome and of the autosomes may also be detectable during early meiotic prophase. Sex chromatin may also be detectable in normal males during mitotic prophase in cells other than spermatogonia. This could account for

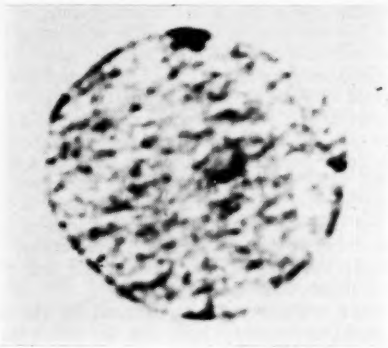

Fig. 2—Germ-cell nucleus disgorged from a seminiferous tubule.
The nucleus, spherical in shape, measuring 20 μ in diameter and with sex chromatin at 12 o'clock, is from a primary spermatocyte in very early prophase. ($\times$ 2000.)

the reported occurrence of sex chromatin in some male somatic cell nuclei. The comparative rarity of meiosis in the normal human ovary and in the testes of subjects with medullary dysgenesis is unfortunate; for in such subjects two sex-chromatin bodies might be visible in the first meiotic prophases.

Further support for the hypothesis that the maximum number of sex-chromatin bodies in somatic nuclei during interphase is one less than the number of X chromosomes comes from a study of the frequency of sex chromatin in somatic cell nuclei.

We have used the formula $1=[nP+(1-n)]^{X-1}$ to predict, in subjects with abnormal karyotypes, the frequency of nuclei with one or more sex-chromatin bodies, where n is the proportion of nuclei which are chromatin positive (P), (1—n) is the proportion chromatin negative, and X is the number of X chromosomes. The values of n and (1—n) are obtainable from normal females and the number of sex-chromatin bodies is given by the index of P. The frequencies in medullary dysgenesis (XXY) are the same as in normal females (XX); and, in subjects with three X chromosomes (XXX and XXXY), the observed frequencies of nuclei which are chromatin double-positive (P^2) chromatin-positive (P), and chromatin-negative are in agreement with the calculated frequencies. The formula is applicable to different techniques of nuclear sexing and to different tissues. It should also be applicable to subjects with more than three X chromosomes.

Summary

Further evidence is presented in favour of the hypothesis that sex chromatin is derived from the heterochromatic segment of a single X chromosome.

Attention is drawn to the presence of a structure, apparently identical with the sex-chromatin body, in normal male germ-cells.

A formula is given for predicting the frequency of nuclei with one or more sex-chromatin bodies in subjects with abnormal karyotypes. This formula is applicable to different techniques of nuclear sexing, to different tissues, and probably to subjects with more than three X chromosomes.

We are indebted to Prof. D. M. Douglas for access to patients under his care.

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Preliminary Communications

A POSSIBLE CAUSAL FACTOR IN INTUSSUSCEPTION IN INFANCY

DESPITE extensive work on the subject, the cause of intussusception in infancy remains undetermined in over 90% of cases.

Any hypothesis must account for the facts (1) that intussusception takes place mainly in the child under twelve months, and (2) that in most cases it starts at, or near, the ileocæcal valve. Perrin and Lindsay [1] pointed out that the amount of lymphatic tissue at the ileocæcal valve, and in the terminal few inches of ileum, was greatest up to one year of age, and thereafter diminished. They suggested that swelling of these tissues could form the apex of an intussusception.

The factors that might produce hyperplasia of the lymphatic tissue are unknown, but there is evidence that infection may be important. A seasonal incidence of intussusception, with peaks in the spring and winter months has been reported,[1 2] and it has been suggested that this may be associated with the seasonal increases in enteric and respiratory infections.[2] In a recent survey of the 285 cases of intussusception admitted to the Sheffield Children's Hospital during 1950–59, we found one peak of incidence during April, May, and June, and another in December and January. Cooke and Lewis[3] noted peaks in the spring and summer months. About one-third of the children had a respiratory infection either on admission or immediately before; and the incidence of this followed very closely the incidence of intussusception. 25 of the children had diarrhœa, but no particular seasonal incidence was noticed.

Recent work suggests a possible infective agent. Rowe et al.[4] first isolated the adenoidal-pharyngeal-conjunctival (A.P.C.) group of viruses from tonsil and adenoid material, and Kjellen [5] isolated viruses of this group from the mesenteric glands and fæces of cases of non-specific mesenteric adenitis.

Since last April we have investigated all cases of intussusception admitted to the Children's Hospital for evidence of virus infection. There have been 16 children, whose ages ranged from three months to four years. 9 of them had a respiratory infection on admission, or in the few days before. All the children were treated by operation, and none of the intussusceptions presented any difficulties in reduction. No specific causative lesion, such as a Meckel's diverticulum, was found, but in each case there was an obvious mesenteric adenitis: severe in 3 cases, moderate in 11, and mild in 2.

A throat swab, specimen of fæces, and a specimen of blood (the acute specimen) were taken on admission. At operation a mesenteric gland was excised for virus studies; and, two to three weeks later, a second specimen of blood was collected (the convalescent specimen).

Over the same period, 84 normal serum specimens were collected from children of corresponding ages. Measurable antibody levels to A.P.C. viruses were found in 37% of them, when estimated by the complement-fixation technique using overnight fix at 4°C.[4]

Detectable antibody was found in the acute serum of only 1 of the children with intussusception—a girl, aged four, who had a two-week history of abdominal symptoms, and who was considered to have chronic intussusception. 11 of the 16 cases had a fourfold diagnostic rise in antibody levels to adenovirus (69%). This is definite evidence of an acute infection with adenovirus, and suggests a primary infection.

In every case where there was serological evidence of infection, adenovirus was isolated from at least one source—throat swab, fæces, or mesenteric gland. In some cases it was isolated from all three sites. The adenovirus was most often found in the fæces. The serotypes of the isolations were I, II, III, V, and VI. Adenovirus was recovered from the fæces in 1 of the 21 controls, who were children of corresponding ages admitted to hospital at the same time as the cases of intussusception, and chosen entirely at random apart from the age factor.

This preliminary study suggests that adenovirus infection in infants may be a significant causal factor in some cases of intussusception. There is no direct proof that it produces hyperplasia of the lymphatic tissue in the intestine, although this seems a reasonable supposition because of the obvious mesenteric adenitis found in all our cases. Virus infection cannot be the sole factor however. The serological results in the control series indicate that adenovirus infection is common in infants; but intussusception is comparatively rare. The incidence in Sheffield is calculated to be 2·27 per 1000 live births. Hyperplasia of the mesenteric and intestinal lymphatic tissue may not be a constant feature of adenovirus infection, or perhaps the occurrence of an intussusception depends partly on other anatomical variants in the ileocæcal region.

Much more investigation is required to answer these questions, but in the meantime further work is proceeding on the prevalence of adenovirus infection in children with intussusceptions, and in other children of similar age.

We are extremely grateful to Mr. R. B. Zachary and Dr. J. L. Emery for their constant encouragement in this work, and for their helpful criticism in the preparation of this preliminary report.

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2. Ravitch, M. M. Intussusception in Infants and Children. Illinois, 1959.
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DISSECTING-MICROSCOPE APPEARANCES OF JEJUNAL BIOPSY SPECIMENS FROM PATIENTS WITH "IDIOPATHIC STEATORRHŒA"

THE introduction of satisfactory methods for biopsy of the mucosa of the small intestine,[1 2] has made possible a study of the histopathology of cœliac disease and "idiopathic steatorrhœa". Microscopic examination of material from adult patients indicates that there are at least two different histological appearances. In many patients with idiopathic steatorrhœa the most striking feature is the flat thick mucosa which is devoid of normal villi; this appearance has been termed "subtotal villous atrophy".[3] In others, the microscopic appearances are different. The glandular layer is thickened, as in subtotal atrophy, but the mucosa shows short broad thickened "villi", varying between 150 and 300 μ in height; to these biopsy appear-

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2. Crosby, W. H., Kugler, H. W. *Amer. J. dig. Dis.* 1957, **2**, 236.
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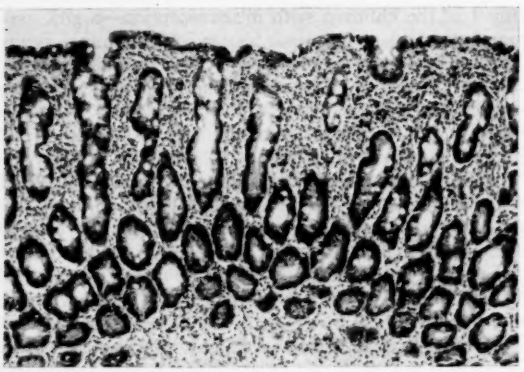

Fig. 1—Section of jejunal mucosa showing subtotal villous atrophy. (× 80.)

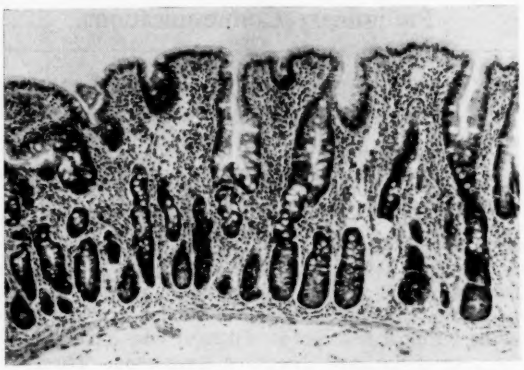

Fig. 2—Section of jejunal mucosa showing partial villous atrophy. (× 80.)

ances the term "partial villous atrophy" has been applied.[3] Fone et al.[4] have confirmed and extended these findings, and have suggested that these differing histological appearances represent at least two causally distinct disorders.

We have examined biopsy material from thirty patients suffering from idiopathic steatorrhœa and have tried to classify this material as showing either subtotal or partial villous atrophy. Although the microscopic examination of histological sections was often adequate for this purpose, we have found that the different appearances of subtotal or partial villous atrophy may be more easily distinguished when freshly obtained samples of jejunal mucosa are examined under the dissecting microscope, a method recommended by Rubin et al.[5] Furthermore, the dissecting microscope reveals the nature of the pathological changes in idiopathic steatorrhœa more clearly than conventional histological techniques alone. The flat appearance of subtotal villous atrophy has been previously recognised using this method [5] but the curious ridged and whorled appearance which we have come to associate with partial villous atrophy has not hitherto been described.

Our purpose here is to report the appearances of jejunal biopsy specimens under the dissecting microscope and to recommend that whole specimens should be routinely examined in this way before histological sections are made. A provisional classification of these appearances is also suggested.

PATIENTS AND METHODS

Intestinal specimens were obtained using the Crosby biopsy capsule [2] the position of the capsule at the time of biopsy being determined radiologically. Mucosal samples were first orientated on a piece of white filterpaper and fixed in 15% formol-saline. They were then examined under a dissecting microscope and photographed. Histological sections were subsequently prepared by conventional techniques.

Thirty patients suffering from "idiopathic steatorrhœa" were studied. All these patients had evidence of intestinal malabsorption without hepatic or pancreatic disease. Intestinal X-rays revealed no gross anatomical lesions of the small intestine in any of them.

RESULTS

Histological Sections

Histological sections of the biopsy material from the thirty patients were classified according to the criteria of Shiner and Doniach.[3]

In sixteen patients, there was unquestionable subtotal villous atrophy, the appearance of a typical specimen being shown in fig. 1. The glandular layer of the mucosa is thickened, and the surface is flat and devoid of villi.

The specimens from eleven other patients showed partial villous atrophy. In these, the glandular layer was also thickened but instead of the flat surface seen in subtotal atrophy, broad short thickened "villi" were present (fig. 2).

Although the examination of single histological sections often sufficed to distinguish between these two types of mucosa, there were three patients in whose biopsy specimens areas of flattened mucosa alternated with thickened "villi". In these patients, as in those whose biopsy appearances are illustrated in figs. 1 and 2, the nature of the mucosal lesion was more clearly revealed by examination under the dissecting microscope.

Dissecting Microscope Appearances

Normal mucosa.—For comparison fig. 3 shows the appearance of the normal intestinal mucosa as seen under the dissecting microscope. Freshly obtained normal mucosa is remarkably beautiful and the long slender villi can be clearly seen. Some of the villi are occasionally broad and leaf-shaped, but the usual appearance is well shown in fig. 3.

Subtotal villous atrophy.—In contrast, biopsy specimens

Fig. 3—Dissecting-microscope appearance of normal jejunal mucosa. (× 35.)

4. Fone, D. J., Cooke, W. T., Meynell, M. J., Brewer, D. B., Harris, E. L., Cox, E. V. *Lancet*, 1960, i, 933.
5. Rubin, C. E., Brandborg, L. L., Phelps, P. C., Taylor, H. C. *Gastroenterology*, 1960, **38**, 28.

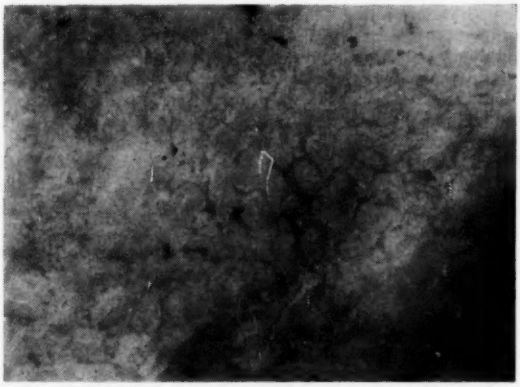

Fig. 4—Dissecting-microscope appearance of jejunal mucosa showing subtotal villous atrophy. (× 35.)
The histological section of this specimen is shown in Fig. 1.

from patients with subtotal villous atrophy were flat and devoid of villi. Fig. 4 illustrates the appearance of part of a typical specimen the histological appearance of which is shown in fig. 1.

The surface of the mucosa was sometimes subdivided by grooves into hexagon shapes, but the most obvious feature in all the patients was the complete flattening and absence of villi.

Partial villous atrophy.—The appearance of partial villous atrophy was strikingly different. An example is illustrated in fig. 5; the histological section of this specimen showing what appeared to be broad and thickened "villi", is seen in fig. 2.

Examination of this specimen under the dissecting microscope (fig. 5) gives a quite different picture of the pathological condition of the mucosa from that suggested by fig. 2. There are no true villi. The entire surface of the intestinal mucosa is made up of a series of ridges, convolutions, and whorls. What appear on histological section to be short and thickened "villi" are in fact transverse sections through these ridges and no villi are seen.

COMMENT

Although it is essential that conventional histological sections of jejunal biopsy material should be examined, it may be more valuable if the appearances under the dissecting microscope are also described. The three-dimensional view obtained by examination of whole specimens may reveal the nature of the pathological changes in the mucosa more clearly than conventional histological techniques.

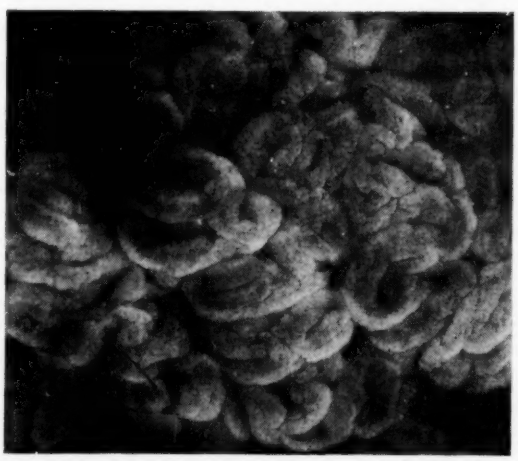

Fig. 5—Dissecting-microscope appearance of jejunal mucosa showing partial villous atrophy. (× 35.)
The histological section of this specimen is shown in Fig. 2.

These different appearances can be classified in purely descriptive terms. The appearance of the normal intestinal mucosa (fig. 3) may be described as "villous", and that of subtotal villous atrophy as "flat" (fig. 4). The curious ridged appearance seen in partial villous atrophy is difficult to describe succinctly, but we suggest the term "convoluted" (fig. 5).

Further studies in larger numbers of patients are being undertaken, and specimens obtained from the ileum are also being examined. In some patients with idiopathic steatorrhœa, whose jejunal mucosa was characteristically abnormal, we have found the ileal mucosa normal, as reported by Rubin et al.[5] We have also seen the "convoluted" appearance in the mucosa of the ileum in two patients whose jejunal biopsy specimens were completely "flat".

We wish to thank Mr. W. Brackenbury for his skill and patience in the preparation of the photographs, and the Medical Research Council for their support. One of us (R. H.) is at present in receipt of a grant from the Medical Research Council.

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AN ATTEMPT TO PRODUCE IMMUNE TOLERANCE TO THYROGLOBULIN IN RABBITS

To explain the presence of autoantibodies to thyroglobulin in Hashimoto's thyroiditis and experimental autoimmune thyroiditis in animals, it has been suggested [1–3] that thyroglobulin, locked in the thyroid, is prevented from establishing immunological tolerance in early life, but if released later can stimulate the production of antibodies. We conducted an experiment to investigate this.

Extracts of rabbit thyroids were injected into rabbits within eighteen hours after birth. When 2 months old, the rabbits were challenged with rabbit-thyroid extract mixed with complete adjuvant, and then bled one month later. The sera were tested for the presence of antibodies against rabbit thyroglobulin. After a second challenge, the thyroids were examined histologically for the presence of thyroiditis, and the sera were again tested for antibodies.

METHOD AND MATERIALS

Antigen.—Thyroid glands from more than 160 adult rabbits were used for the experiment. A crude saline extract was prepared employing a method similar to that of Witebsky and Rose [4] using 20 to 30 thyroids at a time.

Pretreatment of rabbits.—7 litters of rabbits were used. Of the 34 rabbits born, 24 survived the first week. The newborn rabbits were injected intraperitoneally with saline extract of rabbit-thyroid glands within eighteen hours after birth, and

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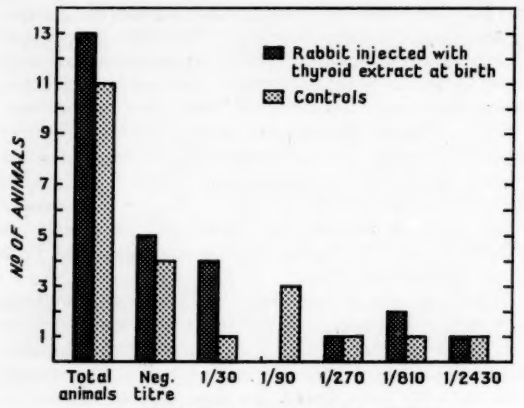

Titre of antibody against rabbit thyroglobulin. Serum was obtained from each rabbit 1 month after the first challenge.

then again five days later. Each experimental rabbit received a total dose the first week equal to the saline extract from the thyroids of 4 adult rabbits. Saline was injected into the control animals, usually littermates.

Immunisation.—All rabbits were challenged at 2 months of age with the same thyroid extract using the procedure of Witebsky and Rose,[4] employing 'Difco' complete adjuvant. The second challenge, which was given between one and a half and seven months after the first, consisted of double the previous dose, given intradermally on the back.[5]

Serological investigations.—The rabbits were first bled just before the first challenge. This was the "zero bleed". They were then bled one month after the first challenge and the sera were tested with tanned cells coated with a crude thyroglobulin preparation according to the method of Roitt and Doniach [6] with slight modifications. Fresh sheep erythrocytes were used. The cells were tanned and coated at 37°C. The saline extract was first made 37% saturated with ammonium sulphate, pH 7·2, and then centrifuged. The supernatant was then made up to 50% saturated with ammonium sulphate and the resulting precipitate washed 3 times in 50% saturated ammonium sulphate, dissolved in buffered saline (pH 7·2), and then dialysed against saline. When this material was subjected to electrophoresis on cellulose-acetate membrane, a large fairly homogeneous spot resulted, which migrated with the α-globulins.

The sera obtained after the first challenge were tested with tanned cells freshly coated with thyroglobulin, while the sera after the second challenge were tested with cells heated similarly, but formolised [7] and stored. Roitt (personal communication) has found no difference between titres obtained with fresh and with formolised tanned cells.

The results were similar throughout, no matter what interval (from one and a half to seven months) elapsed between first and second challenge, or whether the rabbits were killed twenty-four or thirty-five days after the second challenge. These considerations have, therefore, been omitted from the tables.

Histology.—Sections were made of all the thyroids and stained with hæmatoxylin and eosin. Multiple sections were made from all apparently normal glands to ensure that patches of lymphocytic infiltration had not been missed.

5. Rose, N. R., Witebsky, E. *ibid.* p. 417.
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TABLE I—RECIPROCAL OF ANTIBODY TITRES AGAINST RABBIT THYROGLOBULIN AFTER INITIAL CHALLENGE, AND AFTER SECOND CHALLENGE AT WHICH TIME THE THYROIDS WERE REMOVED FOR STUDY

Rabbits injected with thyroid extract at birth				Control rabbits			
Animals	Titre at 1 month after 1st challenge	Titre at time of histological examination	Pathological changes in thyroid	Animals	Titre at 1 month after 1st challenge	Titre at time of histological examination	Pathological changes in thyroid
A1/1	270	7290	++	A1/3	..	..	++
/2	810	7290	++	A2/3	2430	90	−
A2/1	..	270	−	/4	..	Not rechallenged	
/2	30	..	+	/5	90	270	−
A3/2	2430	7290	+	A /3	90	270	+
A4/1	810	7290	++	A /6	90	Not rechallenged	
/2	30	..	+++	A7/3	..	270	++
/3	..	..	−	/4	30	..	++
A5/1	30	..	++	/5	810	7290	+++
/2	..	..	−	/6	270	..	−
/3	..	..	−	/7	..	30	++
A7/1	30	90	+++				
/2	..	7290	+				

RESULTS

Antibodies to rabbit thyroglobulin were not found in the "zero bleed" from any of the rabbits. The presence of antibodies one month after the first challenge is shown on the figure. There was no significant difference between the rabbits injected with thyroid extract at birth and the control animals. The presence of thyroiditis is shown in table I. Again there is no significant difference between the two groups of rabbits. Although animals having antibodies usually had thyroiditis, there were several exceptions in both groups. These are summarised in table II.

TABLE II—RELATION BETWEEN ANTIBODY TITRE AND PATHOLOGICAL CHANGES IN THYROID GLAND IN CONTROL AND TREATED RABBITS. ONLY THE TITRE AT THE TIME THE THYROID WAS REMOVED IS CONSIDERED, UNLESS OTHERWISE STATED

—	Rabbits injected with thyroid extract at birth	Control rabbits
Total with pathological changes	9/13	6/9
Positive final titre with pathological changes in thyroid	6/13	4/9
Negative final titre with no pathological changes in thyroid	3/13	1/9
Negative final titre with pathological changes	3/9	2/6
Positive titre with no pathological changes	1/4	2/3
Negative titre which became positive (3 of the 4 positives were 270 or more)	2/5	2/3
Positive titre which became negative (all were low titres of 30; all 3 however had (+) pathological changes)	2/8	1/6

DISCUSSION

There are several possible explanations for the failure to produce tolerance in the above experiment:

1. The thyroid extract may have to be injected into the rabbits before they are born.

2. Possibly not enough thyroid extract was given during the first week, although the equivalent of the extract from 4 adult thyroids for each newborn appeared to be a large amount.

3. Thyroglobulin may be rapidly metabolised, and should be continued in small doses for a longer period than in the experiment. Animals may have initially been made tolerant but have lost tolerance by the time they were challenged.

4. Adjuvant may play a role in breaking tolerance.

5. Thyroglobulin itself may not be able to produce immunological tolerance although it can stimulate the production of antibodies.

6. Tolerance to thyroglobulin, if produced, may be easy to break.

We are conducting experiments to test possibilities 2, 3, and 4 by administering heterologous thyroglobulin in large doses to newborn rabbits over a ten-day period and then continuing with smaller doses for several weeks.

7. Fulthorpe, A. J. *J. Hyg., Camb.* 1957, **55**, 455.

The use of a foreign thyroglobulin will make the use of adjuvant for challenge unnecessary—at least for the production of circulating antibodies. Until results of such experiments are known, more speculation seems untimely.

SUMMARY

Saline extract of rabbit thyroids injected into newborn rabbits did not prevent the rabbits from later producing antibodies to thyroglobulin or from having thyroiditis in response to a challenge of thyroid extract and complete adjuvant.

We are grateful to Dr. L. E. Glynn for reading the sections of the thyroids for us, and to Dr. I. M. Roitt for having taught one of us (J. R. D.) the hæmagglutination technique and method of preparing the crude thyroglobulin. We are also grateful to the Glaxo Laboratories, the National Institute for Research in Dairying, and the Postgraduate School of London for making rabbit thyroids available to us. This investigation was supported (in part) by a traineeship grant, AT-413 (to J. R. D.), from the National Institute of Arthritis and Metabolic Diseases of the National Institute of Health, United States Public Health Service, and by the Medical Research Council.

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ADRENOCORTICOTROPHIC ACTIVITY IN THE PLASMA OF PATIENTS WITH CUSHING'S SYNDROME ASSOCIATED WITH PULMONARY NEOPLASMS

THE clinical picture of Cushing's syndrome has been reported in association with a variety of neoplasms, most often pulmonary but occasionally thymic or pancreatic.[1–3] Sometimes hyperfunction of the adrenal cortex is noted before the carcinoma is discovered, while sometimes the neoplasm appears first.[2] When the neoplasm appears first, there is no means of knowing whether the cancer stimulates the adrenal cortex directly or via the adenohypophysis,[1] or indeed whether the coexistence of the two conditions is merely fortuitous. In one case adrenocorticotrophic activity was sought in tumour tissue but was not found.[2]

An earlier study[4] demonstrated corticotrophic (i.e., adrenal weight-maintaining) activity in the plasma of patients who had Cushing's syndrome with bilateral adrenal cortical hyperplasia. Such activity could not be detected in three patients with adrenal cortical carcinoma. The data have been interpreted as suggesting that an extra-adrenal substance (perhaps pituitary or hypothalamic) having corticotrophic properties might be related to the ætiology of adrenal cortical hyperplasia, whereas adrenal carcinoma has been assumed to be largely independent of adenohypophyseal influence.

In the present investigation, an attempt was made to determine whether corticotrophic activity was present in the plasma of patients in whom Cushing's syndrome appeared to be the sequel to a neoplasm, and whether mechanisms like those at work in "ordinary" Cushing's syndrome could explain this special form of the disease.

INVESTIGATION

Measurements of plasma corticotrophin were made in three patients, two having adrenal cortical hyperfunction that followed the appearance of bronchogenic carcinoma, and one having a proved carcinoma of the adrenal.

A.B. was a Negro woman, aged 50, in whom the clinical features of Cushing's syndrome were noted $1^1/_2$ months after a left upper-lobe lesion had been discovered by X-ray. When diagnosis of the chest lesion was first made, her appearance was normal, as was her fasting blood-sugar level; but some 45 days later she had rounding of the face, acne, and overt diabetes mellitus. Urinary 17-ketosteroids were 50 mg. per 24 hours, and urinary 17-ketogenic steroids 90 mg. per 24 hours. Plasma 17-hydroxycorticosteroid concentration was repeatedly found to be raised (115-120 μg. per 100 ml.) and did not respond to corticotrophin (A.C.T.H.) stimulation (85 μg. per 100 ml.).[5] Adrenal tumour seemed unlikely because there was no suprarenal mass on retroperitoneal pneumography, and because urinary 17-ketogenic steroid levels responded to administration of the amphenone derivative, SU. 4885.[6]

About 3 months after the initial chest finding, jaundice was observed, and liver biopsy showed metastatic carcinoma. A striking clinical feature was hypokalæmic alkalosis (serum-potassium 2·2 mEq. per litre; CO_2, 40·9 mEq. per litre).[2 3] At necropsy, metastatic carcinoma of bronchogenic origin was found. The adrenals were hyperplastic.

B.C. was a housewife, aged 57, with a 6-month history of cough. Biopsy of a cervical lymph-node revealed carcinoma (cardinoid) of unknown site. No stigmata of Cushing's syndrome were obvious. Over the next 4 months, she complained of back pain and noticed a striking redness of the face and neck. The findings were now typical of hyperadrenocorticism and X-rays of the skeleton showed osteoporosis which had not been present 4 months before. Urinary 17-ketogenic steroids were elevated (35–42 mg. per 24 hours) as were plasma 17-hydroxycorticosteroid concentrations (43 μg. per 100 ml.) which rose excessively after corticotrophin stimulation (80 μg. per 100 ml.).[5] Adrenal tumour seemed unlikely in view of the exaggerated response to corticotrophin,[5] the response of urinary 17-ketogenic steroid levels to SU. 4885,[6] and the failure to demonstrate a suprarenal mass by retroperitoneal air insufflation and radiography. 10 months after the onset of cough, bronchoscopy showed a lesion of the left lower lobe bronchus, which histologically resembled a carcinoid tumour.

C.D. was a man of 38 with plethora, round face, œdema, hypertension, raised postprandial blood-sugar (159 mg. per 100 ml.) and hypokalæmic alkalosis. Urinary 17-ketogenic steroid levels were high (44 mg. per 24 hours), and plasma 17-hydroxycorticosteroids (32 μg. per 100 ml.) did not rise significantly after corticotrophin (36 μg. per 100 ml.).[5] Surgical exploration showed invasive carcinoma of the right adrenal. Necropsy revealed widespread metastases.

In all three patients, corticotrophic activity was assessed by a modification[4] of the adrenal weight-maintenance assay of Simpson et al.[7] The end-point is prevention of adrenal atrophy in the hypophysectomised rat.

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ADRENAL WEIGHT-MAINTAINING ACTIVITY IN PLASMA OF PATIENTS WITH CUSHING'S SYNDROME

Patient	Injected animals			Control animals				
	Animals	Mean paired adrenal weight (mg.)	S.D.	Animals	Mean paired adrenal weight (mg.)	S.D.	t*	p
A.B. ..	6	12·4	0·60	13	10·3	1·26	2·84	<0·02
B.C. ..	4	12·2	1·49	,,	,,	,,	2·54	<0·05
C.D.† ..	6	9·6	0·48	,,	,,	,,	1·30	>0·10

* Value of t computed by assuming equal variability in the injected and control groups of animals.
† A 38-year-old man with Cushing's syndrome following carcinoma of the adrenal.

Male Sprague-Dawley rats were hypophysectomised at 30 days of age. 1 day later, injections of patients' plasma were begun at a dose of 1·0 ml. per day and continued for 9 days. On day 10 (40 days of age) the rats were killed, the adrenals were dissected free, trimmed, and wet-weighed, and the mean paired adrenal weight of injected rats was compared with that of untreated controls.[4]

In patients A.B. and B.C., plasma was shown to have corticotrophic activity—i.e., its injection partially prevented adrenal atrophy in the hypophysectomised rat. Mean paired adrenal weight of treated animals was 12·4 and 12·2 mg. as compared with 10·3 mg. in the untreated controls, these differences being significant at the 2% and 5% level (see table). In contrast, plasma of patient C.D. (adrenal carcinoma) did not prevent adrenal atrophy.[4]

COMMENT

The finding of corticotrophic activity in the plasma of two patients whose adrenal cortical hyperplasia followed the appearance of a pulmonary neoplasm does not, of course, explain the origin of the abnormal corticotrophin. It does, however, suggest that the mechanism of pathogenesis may be the same as, or at least similar to, those operative in adrenal cortical hyperplasia without associated neoplasm. A possible sequence of events would be that by unknown means the carcinoma stimulates an excessive secretion of corticotrophin by the adenohypophysis,[1 2] and that this induces hypersecretion of cortisol by the adrenal cortex.

It is not yet clear whether the substance responsible is an abnormal corticotrophin, as postulated earlier,[4] or "orthodox" corticotrophin as suggested by Nugent et al.[8] and as found in certain patients with adrenal cortical hyperplasia *after* adrenalectomy.[9] The possible adenohypophyseal (or hypothalamic) origin of this corticotrophin is under investigation in studies of the plasma of patients with adrenal cortical hyperplasia before and after successful irradiation of the pituitary.

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CHANGES IN FATTY-ACID COMPOSITION OF HUMAN AORTA ASSOCIATED WITH FATTY STREAKING

PREVIOUS studies of lipids believed to be associated with the development of atherosclerosis and coronary-artery disease have dealt with the late stages of the disease. James et al.[10] investigated the fatty-acid composition of plasma-lipids from both human subjects who had had at least one infarct and controls of the same age. The only demonstrable difference between the two groups was found to be in the degree of unsaturation of the neutral-fat fraction (cholesterol esters and triglycerides), the patients having a higher level of oleic acid. No difference could be detected in the combined level of linoleic and linolenic acids.

Many reports have been published on the fatty-acid composition of cholesterol esters from plasma and atheromatous tissue.[11–15] The later workers in particular showed that the cholesterol-ester fatty acids of atheroma were more highly unsaturated than those from normal tissue. We have confined ourselves to study of the differences in lipid levels and composition between aortal fatty streaks and adjacent normal tissue of the same aorta. This approach was chosen since the fatty streak is believed to represent the first stage of the changes of the aorta that can lead to atheroma.[16] To be able to recognise such changes more clearly, and to remove from consideration the possibility that differences found could be due to differences in the exposure of the normal and abnormal tissue to different blood constituents, it was decided to restrict comparisons between samples obtained from the same aorta.

Our results in these studies were first reported in part at the meetings of the American Society for the Study of Arteriosclerosis in 1958. These data amplify the earlier report. More detailed studies will be reported elsewhere.

Methods

The aortæ were removed from five subjects at necropsy. Age, sex, and cause of death are shown in table I.

The normal and fatty streaked areas were ringed and labelled by one of us (R. L. H.) with black ink. The surface of the aorta was then photographed to show the relationship of the sections. The areas to be studied were then cut out, as well as representative samples preserved for histological study. The normal tissue samples and the abnormal samples from a single aorta were grouped. The tissue studied was obtained from several points along the aorta's length, and the results obtained can be considered as representing an average of the abdominal and thoracic regions.

The samples were preserved at low temperature until required. The intima was removed by stripping after alternate freezing and thawing; the tissue was broken up in a 'Lourd's Blender', and the lipids were extracted with 2:1 chloroform-methanol. Non-lipid material was removed from the extract by the procedure described by Folch et al.[17] Cholesterol esters, triglycerides, and phospholipids were isolated by chromatography on silica-gel columns, using the solvents described by Barron and Hanahan.[18] The cholesterol-ester fraction was free of a fraction which is eluted before the cholesterol esters and the triglycerides which follow. Cholesterol was assayed by the usual digitonin precipitation followed by the Liebermann-Burchard reaction.[19] Triglycerides were assayed by the chromotropic-acid procedure as modified by Van Handel et al.[20]

Saponification was done with 5% potassium hydroxide in 85% alcohol for two hours under reflux. The fatty acids obtained after saponification were esterified in anhydrous methanolic hydrochloric acid, and the methyl esters isolated were analysed by gas-liquid chromatography on both 'Apiezon L' and poly-ethyleneglycol-adipate columns.[21]

Results

Table II shows the fatty-acid composition (major components only) of cholesterol esters, triglycerides, and phospholipids from the intima and media of normal and abnormal tissue taken from the aorta of a coloured

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TABLE I—PORTION (%) OF FATTY ACIDS COMPRISING CHOLESTEROL ESTERS IN INTIMAL TISSUE

Case no.	Sex	Age (yr.)	Oleic acid in		Palmitic acid in		Total (%) unsaturated esters		Cause of death
			Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
1	WM*	30	16·2	39·8	15·9	13·3	45·8	75·0	Gastritis
2	WM	24	21·9	55·7	23·5	9·4	56·2	85·5	Accident
3	CF†	18	16·5	37·5	19·2	9·6	57·6	77·7	Cardiac arrest
4	WM	43	23·0	44·0	16·6	16·5	70·0	75·9	Accident
5	WM	43	28·1	33·9	26·3	14·1	59·3	79·0	,,

* White male. † Coloured female.

female, age 18. It can be seen that the major difference between the normal and abnormal tissue lies in the cholesterol-ester fatty acids of the intima. In this fraction oleic acid is much higher in the streak than in the normal tissue (37·5%, against 16·5%). Linoleic acid is almost identical in the two parts of the tissue. Long-chain polyunsaturated acids showed little change.

The triglycerides of the intima showed practically no change, but the phospholipids of the abnormal intima contain more saturated acids.

So far as the medial lipids are concerned the changes observed are in the same direction as those from the intima but are smaller.

The major changes of composition seem to be limited to the oleic-acid and palmitic-acid esters of the cholesterol-ester fractions studied. We are therefore, for simplicity of presentation, reporting only the percentage composition of these acids and the total percentage of unsaturated fatty acids for the other four specimens studied. Their aortæ, as well as that of the female about whose case data are shown in table I, can be considered as falling into class I as described by Böttcher et al.[22] The summarising data on the five aortæ are given in table I.

The data show clearly that there was a decrease in saturated acids in all cases, and an increase up to threefold in oleic acid in all cases, and that in general the fatty acids of the cholesterol esters of the streak are more highly unsaturated than those found in the normal tissue. In one subject (not shown in the tables) there was slightly less linoleic acid in the fatty streak than in the normal tissue.

Discussion

The results reported here are in general agreement with those reported by Wright et al.,[13] Smith,[14] and Böttcher et al.[15–22] in their analyses of aortæ at a comparable stage of atheromatosis. These workers also report an increment in cholesterol titre primarily due to the accumulation of the esterified form. This facet has been studied intensively by one of us [23] in work which leaves little doubt that the most notable change reported to date in the lipids of the fatty streak, as compared with the lipids of the normal tissue, is the increment of cholesterol-ester concentration.

The present data refer specifically to the composition of the fatty acids esterified to cholesterol as these esters were obtained from normal and fatty streaked portions of a single aorta. As the tables show, cholesterol esters obtained from fatty streaks were marked by an increase (as great as threefold) in the percentage of oleic acid in the fatty-acid population as compared with the fatty acids esterified to cholesterol obtained from normal tissue. Furthermore this increment is liable to be accompanied by a significant decrease in the palmitic-acid concentration (four out of five cases). In every case the total percentage of unsaturated acids in the cholesterol esters of abnormal tissues is greater than the percentage found in the normal tissue.

Summary

At the fatty-streak stage of atherosclerosis, differences in lipid composition can be demonstrated between the streak and adjacent normal tissue. These are largely limited to the intima.

Fatty acids derived from cholesterol esters of a fatty streak are more unsaturated than those from normal areas. The increase in the unsaturated-fatty-acid population is usually greatest in the oleic-acid portion. The drop in the unsaturated portion is usually greatest in the palmitic-acid fraction.

It is not possible at this stage to determine whether these changes are due to alterations of cell permeability to plasma-lipids or to alterations in fatty-acid synthesis or degradation within the intima itself. But, since the differences found are between normal and abnormal

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TABLE II—CASE 3: PERCENTAGE FATTY-ACID COMPOSITION OF LIPID FRACTIONS FROM ADJACENT AREAS OF NORMAL AND FATTY STREAKED TISSUE

Acid	Intima*						Media*					
	Phospholipids		Chol. esters		Triglycerides		Phospholipids		Chol. esters		Triglycerides	
	Norm.	Fatty	Norm.	Fatty	Norm.	Fatty	Norm.	Fatty	Norm.	Fatty	Norm.	Fatty
12 : 0	0·2	0·5	0·5	0·3	1·1	0·1	0·2	0·6	0·3	0·2	0·2	0·1
14 : 0	2·4	2·9	2·6	2·2	5·1	5·8	1·4	1·6	1·0	0·8	2·5	3·1
16 : 0	22·4	21·2	19·2	9·6	17·1	22·8	21·2	22·4	14·5	14·4	29·0	28·9
18 : 0	37·7	47·8	8·3	1·4	9·5	11·0	26·9	32·2	3·1	3·1	7·2	6·5
16 : 1	1·2	1·1	2·6	3·8	3·0	4·5	1·6	1·2	7·0	2·3	2·8	2·7
18 : 1 (oleic)	5·9	3·7	16·5	37·5	22·6	22·9	11·2	11·7	9·7	22·3	39·7	38·7
18 : 1 (isomers) ..	2·9	0	·0	0	0	..	1·5	1·6	0·7	1·7	0·4	3·7
18 : 2–3	3·3	1·2	20·1	17·6	9·6	8·1	3·1	3·4	14·7	14·0	11·2	13·3
20 : 4	1·0	1·8	1·0	Trace	0	0	8·2	5·0	2·0	2·6	0·2	0·1
Other polyunsat. acids of chain length C_{20}–C_{22}	17·4	13·7	17·4	18·8	0	0	19·4	15·4	35·6	31·9	6·3	1·5
Total unsaturated acids	31·7	21·5	57·6	77·7	35·2	35·5	45·0	38·3	69·7	75·8	60·6	60·0

* Major components only.

tissue taken from a *single* aorta, the factor initiating the difference clearly resides in the area of the aorta where the fatty streak is found.

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†Dr. Holman has died since this work was completed.

New Inventions

A SIMPLE ELECTRODE SYSTEM FOR MEASURING pH OF BLOOD

ONE of the difficulties in measuring the pH of blood is that, on exposure to air, loss of dissolved CO_2 causes the pH to fall rapidly. The Stadie electrode [1] was designed in 1931 to minimise exposure to air, but it is fragile, difficult to clean, and difficult to maintain at 38°C, and the concentrated KCl solution tends to jam the tap. Several other electrode assemblies have been introduced since then, but they are all difficult to make, and rather expensive to buy. I here describe a simple apparatus which can be made without any skill in glass-blowing. It is robust and easy to clean; it can be immersed in a waterbath, and it is very cheap to make. Hence it is particularly suitable for student classes. In this laboratory for the past 6 years the apparatus has given no trouble.

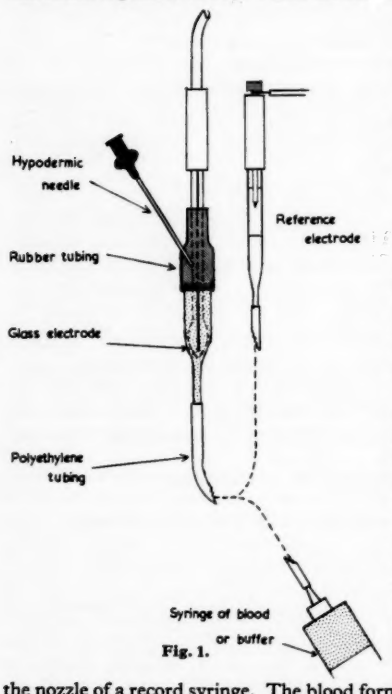

Fig. 1.

The glass electrode (fig. 1) is of the robust spear type (soil electrode, Pye no. 11128). The reference electrode is a standard saturated calomel half cell (Pye no. 11161), which has much the same external diameter as the nozzle of a record syringe. The blood forms its own bridge. The chamber containing the blood—either part of a broken 2 ml. pipette or drawn from glass tubing just large enough to fit over the glass electrode—is connected to the reference electrode by clear plastic tubing so that one can easily see whether it is clean or if bubbles are included. The internal diameter of the plastic tubing is 3 mm.

In use (fig. 2) the apparatus is washed out with buffer solution, then filled with it from a syringe through the plastic tubing, and plunged into a waterbath up to the level of the rubber tubing (the calomel half cell is not immersed). The pH meter is adjusted. The apparatus is then removed from the waterbath, disconnected from the reference electrode, and washed with distilled water through the hypodermic needle. It can be dried with acetone and air but this seems unnecessary. The operator next blows his own alveolar air through this needle, and attaches the syringe containing blood to the polyethylene tubing, which is of such an internal diameter as to fit tightly over the nozzle of the syringe. Blood is then introduced up to the level of the rubber tubing; this requires about 1·5 ml. of blood. The only air to which the blood is exposed is alveolar air, and the exposed blood passes well beyond the sensitive part of the glass electrode. Excess water retained in the assembly floats on the surface of the blood. The syringe is detached and the plastic tubing is slipped over the reference electrode. The apparatus is returned to the water bath and the pH is read 2–3 minutes later. After this the blood can be washed out with saline introduced through the hypodermic needle, and the saline can be replaced by distilled water while the electrode is stored between use.

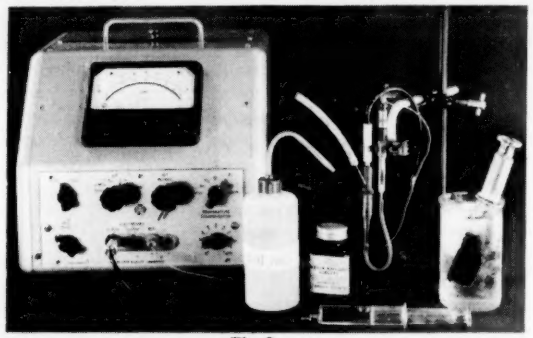
Fig. 2.

The only theoretical drawback of this simple apparatus is that if the reference electrode is left for long in contact with buffer solution or blood, the KCl solution might become desaturated. This does not happen in ordinary use, and in any case it is simple to renew the solution daily or weekly.

I am grateful to the department of photography of the University of Durham for fig. 2.

The Medical School, King's College, Newcastle upon Tyne, 1

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1. Stadie, W. C., O'Brien, H., Laug, E. P. *J. biol. Chem.* 1931, **91**, 243.

A FILTER FOR ATTACHMENT TO A SYRINGE

THIS device is a means whereby a solution or suspension may be drawn into a syringe and expelled through a filter. As shown in the figure, the filter chamber has two parts (*a*) an internally threaded cup with a nozzle which fits standard needles, and (*b*) an externally threaded plug with a concave face. This plug screws into (*a*), and is fitted to a Luer-lock syringe via a two-way tap. The filter screen is a disc of stainless-steel mesh between two silicone-rubber washers which fit inside (*a*), and seal the chamber when the two parts are screwed together. The screen may be of any mesh size suitable for the filtration required. The filter was primarily intended for filtering fat and bone spicules out of bone-marrow suspensions. It was made of brass, and was later chromium-plated.

The filter.
Internal diameter 2 cm.; depth 1·3 cm., thread B.S.P. 14.

It is a pleasure to acknowledge the technical assistance of Mr. G. Brooks in the construction of the filter.

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N. F. ANDERSON M.B. Edin.

Reviews of Books

Growing Old in a Mechanised World

The Human Problem of a Technical Revolution. F. LE GROS CLARK, M.A. London: The Nuffield Foundation. 1960. Pp. 134. 7*s.* 6*d.*

THIS study of the impact of modern industrial technology on the elderly worker is likely to produce great changes in attitudes to retirement from work in industry. Hitherto official policy in this country, with its need for ever-increasing productivity and with shortage of labour, has emphasised that the elderly worker should remain in his job as long as he can; and those who have written about retirement agree that it is best postponed as long as possible. The elderly craftsman, slower perhaps than in his prime, but still able to exercise his creative skill in old age, has been seen as the symbol of happy adjustment to advancing years. Mr. le Gros Clark has made a detailed study of the workings of a number of technologically advanced industries, and he shows that such a picture no longer fits the conditions of the modern factory. Work is geared to the pace of the mechanised production line. Advancing years, even in perfectly healthy people, bring a slowing of mental and physical powers which eventually prevents a man from keeping pace with the machines and with his colleagues. Most modern industries have very few light jobs to offer the elderly worker at this stage, and what jobs there are in this category are largely reserved for younger workmen recovering from illness or injuries. In the public services and non-manufacturing industries there is rather more chance for the elderly worker to reduce his activities gradually, but there is little opportunity for such a man to transfer to this kind of work from outside, and in productive industry retirement at 65 is the rule.

Most men, however, can expect to enjoy some ten years of reasonable health after retirement. This is a new phenomenon, and our society has not yet come to terms with it. The years of retirement and old age are a normal part of the human life-cycle; they last as long as the average man's schooldays, and are no less important to him. We need to recast our social values, to discover the meaning of this phase of human life. Mr. le Gros Clark suggests that one result of such a reappraisal is likely to be an altered distribution of the national income to give a larger share to those who are retired. A man's pension, he says, should be sufficient not merely for his basic needs, but for the maintenance of a respected social life. He should be able to dress properly, to maintain his house and its equipment, to travel and correspond freely, and to fulfil the normal obligations of friendship and hospitality.

This book is an important example of the increasing amount of thought and research now devoted to the problems of retirement, and we hope it will contribute to major changes in social policy.

The Treatment of Tropical Diseases

W. H. JOPLING, M.R.C.P., D.T.M. & H., senior hospital medical officer, Hospital for Tropical Diseases, London. Bristol: John Wright. 1960. Pp. 210. 20*s.*

ONE of the things which makes tropical medicine fascinating is that for most of the diseases within its range there are known causes, many of them protozoal, helminthic, or bacterial. This has encouraged those working in the subject to devote much time and energy to discovering drugs that will eradicate these organisms and to investigating the best ways of giving them. This activity has been intense and is constantly leading to therapeutic and chemoprophylactic advances. It is not easy to keep pace with them, and it is a useful service to bring them together in this small volume. In its construction much work has clearly been done in reviewing the recent literature. Where several remedies are available, it is not to be expected that the author's choice will necessarily be that finding favour elsewhere, but the alternatives are fairly stated.

This book should prove valuable to those in tropical practice, but, as in all books on therapy, its value depends on prior accurate diagnosis without which even the most valuable drugs merely confuse. Properly used, this book will serve a useful function.

Mary, Queen of Scots: the Daughter of Debate

Sir ARTHUR MACNALTY, K.C.B., M.D., F.R.C.P., F.R.C.S. London: Christopher Johnson. 1960. Pp. 247. 21*s.*

As James the Fifth of Scotland lay dying of the consumption which was part of the dowry his first wife, Madeleine de Valois, had unwittingly brought him, a messenger arrived with word of her successor's confinement. The Stuart dynasty needed a male heir, but when James asked hopefully "A boy prince?" the messenger shook his head. The curse with which the king received this news was almost the last thing he said.

His daughter thus became Queen when she was eight days old, and it was an inauspicious start to a life that was beset with ill-health and tragedy to its end, in the castle of Fotheringay, by three badly aimed blows from the executioner's axe.

Sir Arthur MacNalty here reviews, in a very interesting way, Mary's forty-five years, and shows how often she was incapacitated by peptic ulcer, arthritis, and either hysteria or a psychosis. His analysis does not suggest, though, that these disabilities changed the course of Scotland's history. Rather, it seems, they were the reaction of the patient to the times in which she lived. And, since a stronger character might have altered the pattern of events, and not have been broken by it, one wonders whence the weakness in the queen's character derived.

Sir Arthur advances no such theory, but a Freudian might look for some traumatic episode in infancy. Yet Mary enjoyed a happy and reasonably secure childhood. There was, of course, the occasion of her coronation when, only ten months old, she was taken from her nurse and submitted to the ordeal of a long ceremony. During it her hand was closed about a sceptre, and a sword was even girded about her. It is not surprising that the child, finding herself amidst strangers, was terrified, or that she is reported to have cried bitterly throughout. Perhaps a psychiatrist could, with an implication the poet never intended, ". . . say, Here starts the road that leads to Fotheringay".

A Symposium on Industrial Pulmonary Diseases

Editors: E. J. KING, D.SC., F.R.I.C.; C. M. FLETCHER, C.B.E., M.D., F.R.C.P., Postgraduate Medical School of London. London: J. & A. Churchill. 1960. Pp. 273. 32*s.*

THE purpose of a symposium on industrial chest diseases held in London in 1958 was "to cover the whole field of the pneumoconioses as seen in this country in all their aspects, from the physics and biological fate of dust, through experimental, pathological, physiological and epidemiological studies to the radiological and clinical investigation and treatment of the patient." The editors of the proceedings add that "it may appear to the reader that a disproportionate emphasis is placed on coalworkers' pneumoconiosis"; and they attempt to justify this by saying that it is the most prevalent and serious form of pneumoconiosis in industrialised countries throughout the world and that it has been more intensively studied than any other pneumoconiosis. This statement is questionable: for one thing, there are industrialised countries where coalworkers' pneumoconiosis does not dominate the picture, notably in South Africa, Australia, Italy, and Scandinavia. It is true that in Great Britain, France, Belgium, and Germany coalmining has been studied more intensively, so that other important pneumoconiosis-producing industries may have been overshadowed. The book, therefore is mainly about the various aspects of the effects of coal dust on the workers' lungs with incidental references to other dusts and other industries.

Meiklejohn's opening chapter on industrial pulmonary diseases in Great Britain is devoted almost exclusively to coalmining; and the pathology, as described by Gough and Heppleston, is largely that of coalworkers' pneumoconiosis, though they do include notes on asbestosis, a disease which is more serious than the other pneumoconiosis and which could

have been dealt with at greater length. Further reference, however, is made to asbestosis by Doll in his chapter on occupational lung cancer. There are no less than three chapters on the important subject of lung-function tests, one each by Hugh-Jones, Gilson, and McKerrow, and each chapter is useful and ably written.

King and Harrison's brief chapter on the experimental production of pneumoconiosis refers mainly to coal and quartz dusts and the modifying effects of infection; and Cochrane deals with the epidemiology and Ball with the treatment of coalminer's pneumoconiosis. Caplan's syndrome, with special reference to coalminers, is appropriately and adequately discussed by Caplan himself. Simon, in a short dogmatic chapter, deals with the problems of taking and reading chest radiographs, and the title of Fletcher's chapter ("the radiological diagnosis of pneumoconiosis") implies that a diagnosis can be made solely on the basis of an X-ray film. He also discusses the classification of the X-ray appearances and emphasises the preoccupation of experts on coalworkers' pneumoconiosis with nodular shadows to the exclusion of the linear and reticular ones. Chapman discusses X-ray technique and the use of radiography in the field.

Nagelschmidt's review of the theories of silicosis is concise and authoritative, and Davies' chapter on the deposition of dust in the lungs is a good presentation of the physics of the behaviour of dust particles, and not only of coal dust.

The "odd men out" of this symposium on coalminers include Hale on pneumoconiosis in Cornwall (but why not Cumberland, or Yorkshire, or even Staffordshire?); Schilling on the epidemiology of byssinosis; Robertson on tin oxide; and McLaughlin on iron and other radio-opaque dusts. Higgins deals with bronchitis in agriculture, mining, and foundries, and Hunter winds up with an entertaining chapter on the prevention of silicosis.

Doctor Agnes Bennett

CECIL and CELIA MANSON. Epilogue by AGNES BENNETT, O.B.E., M.D., B.SC. London: Michael Joseph. 1960. Pp. 189. 18s.

THIS book is of interest from several viewpoints. Dr. Agnes Bennett, who died in November at the age of 88, was a remarkable woman, whose ability and determination have left their mark both in Britain and in New Zealand. This account of her life has chiefly been compiled from her own reminiscences, diaries, letters, newspaper cuttings, and other material, and they give an absorbing picture of a popular and colourful character.

A woman of Dr. Bennett's age, ability, and temperament was inevitably involved in the struggles of women for their rights, particularly the right to be educated and to enter the medical profession. The story of women pioneers in medicine has often been told, but Dr. Bennett was involved not only in Edinburgh but also in Australia and New Zealand. Her disagreements with the leaders of the medical profession in New Zealand, particularly Dr. (later Sir) Truby King, are of particular interest. She devoted most of her life to the improvement of public health and public-health services, and in her life-story many of the great changes of this century are reflected.

Attenuated Infection

The Germ Theory in Contemporary Perspective. H. J. SIMON, M.D., PH.D., assistant professor in medical microbiology and assistant professor in medicine, Stanford University School of Medicine, California. London: Pitman. 1960. Pp. 349. 80s.

THE thesis of this book is that bacterial disease is nowadays seldom due to the introduction of a parasite from without but rather to the pathogenic action of organisms already in the body. These are stimulated to produce disease either by changes in their own virulence or by changes in the resistance of the host produced by external stimuli or by biochemical upsets or the unwise use of antibiotics or steroids. The author illustrates his points lavishly with examples drawn from human, animal, and plant pathology.

The argument is probably a commonplace to most bacteriologists, but this real change in emphasis in the pathology of infectious disease is as yet hardly recognised by many other doctors. This book is therefore timely, but we wish it were less diffuse and more closely argued. The author often obscures rather than illuminates his argument when he extends it to Prince Kropotkin and Herbert Spencer. He omits almost all quantitative data, and without them the study of infection will remain guesswork. Some of his statements are surprising—for example, "The *Clostridia* are a group of . . . bacilli with very little invasiveness". The definitions upon which his argument depends lack precision and are not mutually exclusive; and he is fond of escaping from a logical difficulty by tags about "the exception proving the rule".

These faults are disappointing because there is a real need for a book on this subject and much hard work has gone into this one. As it is, the pertinacious reader will find many valuable nuggets among the pay dirt, but those who would benefit most by reading it will probably abandon the struggle.

Practical Proctology (2nd ed. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 737. 180s.).—Proctology has been elevated to a specialty within the lifetime of Dr. Louis Buie, the author of this book. This transformation has brought in its train a restrictiveness and the creation, almost, of a mystique. The purpose has now been served of raising standards in an area hitherto neglected, and today there is more than a possibility that those following this particular interest may be cut off from the current developments and thought in medicine at large. The second edition of this work retains a highly traditional flavour (tuberculosis, syphilis, and actinomycosis receive prominence, with no mention of Crohn's disease in a chapter on granulomatous disease; factitial proctitis and colitis receive a whole chapter as does melanosis coli). With an emphasis on minutiæ and a tendency to humanistic exhortations, the result is a formidable book.

The Human Blood Proteins (3rd ed. English translation by Harvey T. Adelson, M.D. London and New York: Grune & Stratton. 1960. Pp. 491. Price 111s.).—The first edition by Prof. Ferdinand Wuhrmann and Dr. Charlie Wunderly, of Zürich, appeared in 1947, and much revision and alteration has been needed to bring it up to date. The theme is methods of examination of proteins and their clinical and practical significance. Of the methods, paper chromatography and spectrophotometry have been deliberately omitted. Full details are given of qualitative and quantitative chemical methods and of electrophoresis in all its varieties, including paper electrophoresis and agar-gel methods. A section on ultracentrifuge methods is included. Special tests described fully and clearly include erythrocyte-sedimentation, the Weltmann coagulation band, the nephelogram, and various turbidity and flocculation reactions. The significance and evaluation of these methods is carefully discussed. The authors are still wedded to the idea of "reaction constellations"—i.e., the graphic representation of a standard collection of tests so that any deviation from normal of the pattern shows up clearly, and examples are given of results in many pathological conditions. A special section is devoted to "dysproteinæmias and paraproteinæmias", by which the authors mean conditions like myeloma, macroglobulinæmia, nephrosis, and fibrinogen diseases; the section includes some colour photographs of changes in the bone-marrow in these diseases. Recently discovered protein abnormalities, like the properdin system are included. There are many tables of factual information and analyses of normal and abnormal blood-proteins. The translation, by Dr. Harvey T. Adelson, is good in the technical sections, but less successful in the discussion. The book is well produced and the many electrophoretic diagrams are very clear. In 1947 this book was almost alone in its field, and, though it has now a rather old-fashioned look, it is still worth its place as a reference book for the laboratory shelf.

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Not for Sale

SINCE the inception of the National Health Service all patients in this country have been paying patients, though comparatively few now pay their doctors individually. Like paying patients in former days, they are entitled not only to medical care but also, with one reservation, to the medical care of their own choice. The single reservation—that their choice must not conflict with our professional freedom—has enabled us, through the generations, both to regulate our own affairs and also to impose on those who seek our help a system of bylaws of our own making. This, we believe, is the only way in which we can safeguard our patients' rights; and our professional claim has not yet been seriously disputed. But it would cease to be valid if public and profession were to disagree on what these rights are.

In a letter to the Press, quoted in Parliament,[1] a family doctor declared that " queue-jumping for hospital beds has become a racket "; and, though we agree with the Under-secretary of State that this is not a matter that can be analysed statistically by lay administrators, it is certainly one to be considered by the profession itself. Do we all, in fact, fully recognise that the National Health Service, besides creating a new framework for medical practice, has changed its contractual basis? The change has come because those twin pillars of the pre-war system—public charity and voluntary service—have largely been replaced by financial agreements which in turn have made the hospital consultant no longer a dispenser of private gifts but a guardian of public property. One of the services for which he accepts payment today is the administration of hospital beds; and if he is allowed great freedom in allocating them, his authority rests entirely on the public's trust.

In this country fundamental beliefs are seldom put into words and they are often all the stronger because they lack definition. Before the war the limits of the duty a doctor owed his hospital patients were neither laid down by Parliament nor promulgated by professional committees; yet no doctor and few patients had doubts about them. Similarly, the privileges that could be accorded to those who paid a fee, though undefined, were as easily grasped as the distinction between an act of charity and the fulfilment of a business deal. In this tradition the National Health Service, which recognises two types of paying patient—one public and the other private—gave no instructions about the extra service to which the latter would be entitled; and it could not be expected that the ethics of the new system would at once replace the ethics of the old. Thus it is that the question of free drugs for private patients is still passionately disputed; that we are still burdened with a few absentee consultants whose private practices would wither away if they were conducted on the lines of their outpatient clinics; and that some hospital facilities are still irregularly used for private patients. On the other hand, those who dispute about free drugs do not doubt the sincerity of their opponents; the services of the great majority of consultants make up for the deficiencies of the few; and it can be argued that hospital patients benefit indirectly from the experience and incentive provided by private practice. The truth is that an inarticulate feeling has grown up among doctors that, in a medical scheme defined by law, the regulations must be tempered by common sense; and some of the outward manifestations of this feeling have been in the highest tradition. (We have yet to hear of a surgeon who has cut short an operation, or a physician a ward-round, at the end of his notional half-day; and few would doubt that if hospital staff punctiliously observed the timetable on which their remuneration is based the National Health Service would soon be in difficulties.) Most people have grown accustomed to the idea that a little juggling with the regulations is not only permissible but even perhaps beneficial.

The dangers of rigidity are such that in every large human organisation there should certainly be a little " give ". Even so, however, there surely can be no possible justification for depriving a patient of a hospital bed which he not only needs but which is his by right. To give priority to a patient, not because of clinical urgency but because he has paid a consultation fee, is not an exercise in professional freedom but more nearly an act of conspiracy; and it brings us face to face with the question whether, in an admittedly imperfect organisation, we wish to allow such conspiratorial arrangements to take precedence over public treaties. The cost of supplanting our legal contract with the public by undercover personal liaisons would eventually have to be paid in professional privileges—a currency in which the vast majority of doctors in this country are not prepared to deal. Standards of practice cannot be maintained without professional freedom; and it is in the interest of public as well as doctors that this should not be whittled away. But in the long run our only guarantee that it shall be preserved is public faith in our integrity.

1. See *Lancet*, 1960, ii, 212.

Bretylium and Guanethidine

THERE is argument as to how " essential " primary hypertension is,[1] and this bears on the practical question whether it is ever truly " benign ". But at least there is no doubt that any notable and sustained elevation of the diastolic blood-pressure will have a dangerous impact on vital organs, and that severe diastolic hypertension must be controlled as quickly and safely as possible. Bretylium tosylate (' Darenthin '), introduced in 1959, was found to have the great advantage over the ganglion-blockers that its action in therapeutic dosage was limited to " adrenergic blockade ".[2] For the first time patients

1. Morrison, S. L., Morris, J. N. *Lancet*, 1960, ii, 829.
2. See *ibid.* 1959, ii, 27.

could have a worthwhile diminution in sympathetic vasomotor effect without being subjected to dryness of the mouth, impaired ocular accommodation, and obdurate constipation. A little later reports [3 4] appeared of another hypotensive agent, guanethidine (' Ismelin '), which resembled bretylium in being an adrenergic blocker without significant action on parasympathetic transmission, but which had a more sustained action. These two drugs together represent the most significant advance in hypotensive therapy since the introduction of the ganglion-blockers.

The first clinical report on bretylium [5] showed that severe hypertension could usually be controlled while the patient was in hospital, and that control could be maintained for at least a limited period although increasing doses were commonly needed. The side-effects, such as nasal stuffiness, were comparatively trivial; and patients who had had experience of the ganglion-blockers were glad to be free of the troublesome effects of parasympathetic blockade. But time has brought to light more serious side-effects, such as exertional dyspnœa associated with hypotension,[6 7] muscular weakness and tremor,[8] and distressing mental changes with the larger doses.[9] Moreover, long-term control of hypertension with bretylium has proved difficult, and troublesome to patient and doctor, because of " its transient action, the rapid development of tolerance, and the need to supplement it with chlorothiazide and other agents ".[9]

Guanethidine seems to be free from some of the disadvantages of bretylium. DOLLERY et al.[10] treated 80 patients with guanethidine, and found that " patients did not become resistant to the drug and the hypotension is less variable ". EVANSON and SEARS [9] also found guanethidine superior to bretylium, particularly in long-term control. The most striking early side-effect of guanethidine is diarrhœa, in contrast to the constipation with the ganglion-blockers; indeed, a small dose of pempidine may correct diarrhœa due to guanethidine.[10] Other side-effects include nasal obstruction, bradycardia, parotid tenderness, tremor, weakness,[10] and fluid retention which can be controlled with hydrochlorothiazide.[11] LEISHMAN [11] has also noted transient neurological manifestations in older patients; these may be related to the persistent action of the drug, which should not be administered to patients with symptoms of caroticovertebral stenosis.[12] Unlike the ganglion-blockers, guanethidine does not affect libido or potency, but ejaculation may be delayed or prevented.[13] Although guanethidine, like bretylium, does not alter the effect of noradrenaline and hypertensin,[14] it has proved effective in the temporary control of hypertension secondary to pyelonephritis [13] and to renal-artery stenosis [15]; this accords with the hypothesis that hypertension, once established owing to renal disease, may be perpetuated or aggravated by extrarenal factors.[16] Guanethidine is incompletely absorbed, about 25% of labelled drug being recovered in the fæces after oral administration; in rats the drug was found to be mainly intracellular with a high concentration in the kidneys, as with other organic bases.[10]

With guanethidine hæmodynamic studies have shown the expected decrease in peripheral resistance, without change in pressure or resistance in the pulmonary circulation [14 17]; with bretylium there is a striking increase in the pulmonary vascular resistance, both in the healthy and in the hypertensive.[17] Transient decrease in renal blood-flow, glomerular filtration, urine-volume, and output of solutes has been observed after the intravenous administration of bretylium [17] and of guanethidine [18]; but the oral administration of a small dose (10 mg. daily) of guanethidine to healthy subjects was not associated with any change in inulin clearance or electrolyte excretion.[18]

Guanethidine is at present the drug of choice for the management of severe hypertension; but its use demands care, especially in older patients with established vascular damage. The comparative effectiveness of guanethidine in controlling even secondary hypertension must not lead us to curtail the investigations which are needed to establish the cause of hypertension, particularly in younger patients.[19]

Renal Tubular Acidosis

THE condition termed renal tubular acidosis is impossible to define without a clear knowledge of the renal control of acid-base balance. This subject has unfortunately been complicated by confusion of nomenclature. Many clinical and physiological investigators use the nomenclature popularised by GAMBLE [20] in which the term " acid " is regarded as equivalent to so-called "fixed anions" (e.g., Cl^-, SO_4^{--}, or HPO_4^{--}) and " base " as equivalent to " fixed cations " (e.g., Na^+, K^+, or Ca^{++}). This nomenclature is completely incomprehensible to the pure scientist. Investigators trained in physical chemistry prefer to use the terms introduced by BRÖNSTED,[21] who defined an " acid " as a hydrogen-ion or proton donator and a " base " as a proton acceptor. The difference in outlook is typified by the explanations given for the metabolic acidosis following administration of ammonium chloride and the metabolic alkalosis following ingestion of sodium bicarbonate. Investigators using GAMBLE's nomenclature say that ammonium chloride causes an acidosis by addition of " fixed acid " (i.e., the chloride ion) and

3. Page, I. H., Dustan, H. P. *J. Amer. med. Ass.* 1959, **170**, 1265.
4. Leishman, A. W. D., Matthews, H. L., Smith, A. J. *Lancet*, 1959, ii, 1044.
5. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. *ibid.* p. 17.
6. Turner, R., Lowther, C. *ibid.* 1960, i, 381, 769.
7. Lowe, R. D., Rosenheim, M. L. *ibid.* p. 655.
8. Campbell, E. D. R., Montuschi, E. *ibid.* 1960, ii, 789.
9. Evanson, J. M., Sears, H. T. N. *ibid.* p. 387.
10. Dollery, C. T., Emslie-Smith, D., Milne, M. D. *ibid.* p. 381.
11. Leishman, A. W. D. *German med. Monthly*, 1960, **5**, 361.
12. Hutchinson, E. C., Yates, P. O. *Lancet*, 1957, i, 2.
13. Arnold, O. H., Kaiser, K. *German med. Monthly*, 1960, **5**, 366.
14. Lichtlen, P., Schaub, F., Bühlmann, A. *ibid.* p. 371.
15. Brown, J. J., Owen, K., Peart, W. S., Robertson, J. I. S., Sutton, D. *Brit. med. J.* 1960, ii, 327.
16. Pickering, G. W. *Clin. Sci.* 1954, **5**, 229.
17. Taylor, S. H., Donald, K. W. *Lancet*, 1960, ii, 389.
18. Mertz, D. P. *German med. Monthly*, 1960, **5**, 378.
19. Platt, R. *Quart. J. Med.* 1947, **17**, 83.
20. Gamble, J. L. Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid. Cambridge, Mass, 1951.
21. Brönsted, J. N. *Chem. Rev.* 1928, **5**, 231.

that sodium bicarbonate causes an alkalosis by gain of "fixed base" (i.e., the sodium ion). Physical chemists would take the opposite view: ammonium chloride causes acidosis because ammonium ion (NH_4^+) is a proton donator and is therefore an acid, whereas sodium bicarbonate produces alkalosis because the bicarbonate ion (HCO_3^-) is a proton acceptor and is therefore a base. But, while BRÖNSTED's nomenclature is scientifically more correct, it must admitted that the main advances in research on acid-base balance have been made by investigators using the less correct nomenclature.

Normally the metabolic processes of an average adult produce about 50–60 mEq. of hydrogen ion daily, and, if acidosis is to be prevented, this must be excreted in the urine. Hydrogen ion is eliminated in two forms—(1) as free hydrogen ion measured as urinary titratable acidity; and (2) as ammonium ion (NH_4^+), where hydrogen ion is combined with ammonia. ELKINTON et al.[22] show that normally these two forms are about equally important, excretion of ammonium contributing 39–74% of the total hydrogen-ion output with a mean value of 53·6%. Where metabolic acidosis is produced by ingestion of ammonium chloride, the excretion of ammonium becomes progressively more important: on the third day of acidosis ammonium excretion accounted for a mean of 64·3% of the total hydrogen-ion output, and on the fifth day for 71·4%.

A third important parameter in the renal control of acid-base balance is the maximum urinary acidity. In metabolic acidosis the urine is normally highly acid, with a pH below 5·0. This implies a high gradient of hydrogen ion between the urine and plasma. The average maximal gradient is 800 to 1, corresponding to a urinary pH of 4·6, but some excrete a urine of pH 4·4 with a hydrogen-ion gradient of 1000 to 1. SCHWARTZ et al.[23] showed that in certain unusual experimental conditions a still greater hydrogen-ion gradient between urine and plasma could be produced, the true minimum urinary pH being 4·0. This unusual degree of urinary acidity can be produced by a combination of secondary hyperaldosteronism and infusion of a sodium salt of a non-diffusible anion—e.g., sulphate, phosphate, or *p*-aminohippurate. Aldosterone increases sodium reabsorption in the distal tubules of the kidney. Usually most of the reabsorbed sodium is accompanied by the diffusible anion, chloride. If most of the anion within the tubular lumen is non-diffusible, sodium can be reabsorbed only by the exchange of potassium or hydrogen ion for sodium.[24 25] In the important experiments of SCHWARTZ et al.,[23] the subjects were first rendered sodium and chloride deficient by dietary salt restriction, and then excess isotonic sodium sulphate was infused. The result was urine of record acidity, containing large quantities of potassium sulphate. A highly acid urine facilitates total hydrogen-ion excretion in two ways. First, the titratable acidity, which is roughly inversely proportional to the urinary pH, is increased; and secondly ammonia diffuses more freely,[26 27] and excretion of ammonium is correspondingly enhanced.

WRONG and DAVIES,[28] in a careful study, have defined the differences between the acidosis associated with uræmia, and that in renal tubular acidosis where the blood-urea is normal. In uræmia the synthesis and excretion of ammonium ion is grossly reduced, presumably owing to destruction of a large proportion of the tubule cells. The ability to produce a highly acid urine remains normal or is only slightly reduced, and therefore the titratable acidity is often within normal limits. The fraction of the total hydrogen-ion output which is excreted as ammonium becomes almost zero. Clearance of phosphate and sulphate is reduced as the renal failure becomes more severe, and consequently plasma phosphate and sulphate increase. This causes a secondary reduction of plasma-chloride despite a low plasma-bicarbonate from the acidosis. By contrast, in renal tubular acidosis ammonium excretion is not reduced, and in fact is often above the normal values in relation to the urinary pH. The specific defect in renal function is inability to produce a high concentration gradient of hydrogen ion between urine and plasma, and therefore a highly acid urine cannot be formed. This specific defect could be due either to failure to secrete hydrogen ion at the cation-exchange site in the distal tubule, or to an abnormal permeability to hydrogen ion of the epithelium of the collecting ducts, allowing some of the secreted hydrogen ion to diffuse back into capillary blood. Ammonium excretion therefore accounts for an abnormally high fraction of the total hydrogen-ion output. ELKINTON et al.[22] found that in two cases of the disease this fraction accounted for 70% and 72% of the total. Ammonium output may in fact be so high that compensation is entirely adequate, and such cases will not be acidotic; they are recognised clinically by associated symptoms or signs—e.g., nephrocalcinosis or renal colic. The typical acidification defect becomes obvious after administration of ammonium chloride. The urine does not become highly acid, and more severe systemic acidosis will develop than in the healthy.

In renal tubular acidosis, since the glomerular filtration-rate is normal, plasma sulphate and phosphate are not increased. The plasma-bicarbonate falls because of the systemic acidosis, and therefore the plasma-chloride rises to values considerably above normal. This has led to use of the term "hyperchloræmic acidosis". SMITH [29] has reviewed the incidence of clinical signs of renal tubular acidosis in adults. He found that about 70% of the patients were female. About 50% had osteomalacia, 70% had renal calculi, 75% had nephrocalcinosis, and 45% had evidence of potassium depletion.

Renal tubular acidosis is therefore a condition that can be precisely defined. It may or may not be associated with systemic acidosis and is often accompanied by nephrocalcinosis, renal calculi, osteomalacia

22. Elkinton, J. R., Huth, E. J., Webster, G. D. Jr., McCance, R. A. *Amer. J. Med.* 1960, **29**, 554.
23. Schwartz, W. B., Jenson, R. L., Relman, A. S. *J. clin. Invest.* 1955, **34**, 673.
24. Pitts, R. F., Alexander, R. S. *Amer. J. Physiol.* 1945, **144**, 239.
25. Berliner, R. W., Kennedy, T. J., Orloff, J. *Amer. J. Med.* 1951, **11**, 274.
26. Orloff, J., Berliner, R. W. *J. clin. Invest.* 1956, **35**, 223.
27. Milne, M. D., Scribner, B. H., Crawford, M. A. *Amer. J. Med.* 1958, **24**, 709.
28. Wrong, O., Davies, H. E. F. *Quart. J. Med.* 1959, **28**, 259.
29. Smith, L. H. Jr. *in* The Metabolic Basis of Inherited Disease (edited by J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson). New York, 1960.

or rickets, and evidence of potassium depletion. Early in the course of the disease the blood-urea is within normal limits, but a specific defect of renal tubular function is always present. The kidney is incapable of producing urine of a lower pH than 5·4 (equivalent to a urine/plasma concentration ratio of hydrogen ion of 100 to 1) despite a spontaneous metabolic acidosis or a similar acidosis produced by an adequate ammonium chloride intake—i.e., a dose which will reduce the plasma-bicarbonate to less than 20 mMol. per litre. LATNER and BURNARD [30] found that infusion of neutral isotonic solutions of sodium phosphate in infants with renal tubular acidosis led to production of urine with a lower pH than was possible without such infusion—a situation probably analogous to the physiological experiments of SCHWARTZ et al.[23]

ELKINTON and his colleagues [22 31 32] have published three important papers which can be assessed with this definition in mind. In the first paper they compare the effects of administration of ammonium chloride to 18 healthy subjects and to 5 adults with what they term renal tubular acidosis. Only 3 of these 5 cases are acceptable as examples of this disease if the above conventional definition is accepted. The urine pH of the other 2 patients fell after ingestion of ammonium chloride to 5·18 and 4·72. ELKINTON et al. themselves seem to have doubts of the validity of the diagnosis in the 2nd of these cases, for they say: "In retrospect a diagnosis that seems at least as likely is that of resistance to vitamin D complicated by pyelonephritis." Perhaps most workers would regard the latter diagnosis as much the more likely, though admittedly the differential diagnosis hinges on the definition of renal tubular acidosis. ELKINTON et al.[22] give a less precise definition of renal tubular acidosis as "a constant or intermittent acidosis due to failure of acid excretion by non-contracted kidneys with normal or only moderately impaired glomerular function". They do not specify how it is determined that the kidneys are not "contracted", or exactly what is meant by "moderately impaired glomerular function".

Failure of hydrogen-ion excretion in these patients was assessed by the following "clearance index" of hydrogen ion: the total hydrogen-ion excretion in milliequivalents per minute is divided by the reciprocal of the plasma-bicarbonate expressed in millimoles per litre. This rather complex mathematical expression is identical with the product of the hydrogen-ion output per unit time and the plasma-bicarbonate concentration. The reciprocal was presumably adopted to make the "index" more similar to the "clearance" values of classical renal physiology. Convincing evidence is given that the "clearance index" is a useful means of assessing the ability of the kidney to excrete hydrogen ion. Normally the hydrogen-ion output is about 60 mEq. per day (0·042 mEq. per minute) and the plasma-bicarbonate output 25 mMol. per litre, giving an expected "clearance index" of 1·05. This "index" cannot easily be expressed in definable units. Expressed mathematically its units are M^2/L^3T, in contrast to the clearance formula where the unit is L^3/T, usually expressed in ml./minute. The normal range of the "index" is considerable; ELKINTON et al.[22] give a variation of from −0·5 to 1·75 with a mean of about 1·0. The values are negative if the urine is alkaline, and if urinary bicarbonate exceeds the sum of the titratable acidity and ammonium output. In metabolic acidosis the output of hydrogen ion increases more rapidly than the plasma-bicarbonate falls, and therefore the "index" rises. On the third day of ammonium-chloride ingestion the index in healthy subjects ranged from 1·4 to 3·4 with a mean of 2·07, and on the fifth day from 1·5 to 3·4 with a mean of 2·47. Although there was no segregation of patients from healthy subjects before ingestion of ammonium chloride, there was clear separation both on the third and the fifth day of metabolic acidosis. The "index" test, carefully used, is clearly a useful means of diagnosing reduced ability of the kidney to excrete hydrogen ion, but is not of value in distinguishing the various types of renal acidosis. Administration of ammonium chloride may be dangerous in patients with renal disease. In one of the patients of ELKINTON et al.[22] the arterial total CO_2 fell to 9·9 mMol. per litre, and the arterial-blood pH to 7·24—values which would be an indication for immediate hæmodialysis in cases of acute oliguric renal failure. This series of 5 cases is of especial value in showing that cases of acidosis of renal origin cannot always be rigidly classified into one of the two types described by WRONG and DAVIES.[28]

In the second paper [31] the effects of a single dose of the carbonic-anhydrase inhibitor, acetazolamide, at a dosage of 10 mg. per kg. body-weight, is compared in 4 cases of renal tubular acidosis, 4 cases of uræmia, and 12 healthy subjects, including 2 made acidotic by ingestion of ammonium chloride. The potency of acetazolamide in alkalinising the urine, and in increasing sodium, potassium, and bicarbonate excretion is reduced by metabolic acidosis whether produced by ammonium chloride or by previous doses of acetazolamide itself.[33 34] In all the subjects the response was proportional to the filtered load of bicarbonate. ELKINTON et al. conclude that their results "are consistent with, but neither rule in nor rule out, deficient activity of carbonic anhydrase as one factor in the tubular impairment of proton donation in renal tubular acidosis". YAFFE et al.[35] found a normal content of carbonic anhydrase, glutaminase, and succinic-acid dehydrogenase in a percutaneous renal biopsy from a girl aged 4 with renal tubular acidosis. The activity of triphosphopyridine-nucleotide (T.P.N.) diaphorase, linked to isocitric-acid dehydrogenase in the tricarboxylic-acid cycle, was abnormally low. This result is unlikely to be due to an associated potassium deficiency because the plasma-potassium was normal when the biopsy was taken, and

30. Latner, A. L., Burnard, E. D. *Quart. J. Med.* 1950, **19**, 285.
31. Webster, G. D., Jr., Huth, E. J., Elkinton, J. R., McCance, R. A. *Amer. J. Med.* 1960, **29**, 576.
32. Huth, E. J., Webster, G. D., Jr., Elkinton, J. R. *ibid.* p. 586.
33. Counihan, T. B., Evans, B. M., Milne, M. D. *Clin. Sci.* 1954, **13**, 583.
34. Schwartz, W. B., Danzig, L. E., Relman, A. S. *Amer. J. Med.* 1953, **14**, 526.
35. Yaffe, S. J., Craig, J. M., Fellers, F. X. *A.M.A. J. Dis. Child.* 1959, **98**, 659.

T.P.N. diaphorase is in increased concentration in the kidney of the potassium-deficient rat.[36] The view suggested by YAFFE et al.[35] that the defect in renal tubular acidosis is due to lack of intracellular energy necessary to maintain a high hydrogen-ion gradient and possibly linked with a defect of the tricarboxylic-acid cycle, has more experimental support than a deficiency of carbonic anhydrase. As yet, however, the cause of the specific impairment of renal tubular function is uncertain.

The third paper [32] is a valuable review of published cases of renal tubular acidosis. ELKINTON and his colleagues divide the condition into the primary types, and the cases secondary to the de Toni/Fanconi syndrome, Lowe's syndrome, galactosæmia, nephrogenic diabetes insipidus, Wilson's disease, and chronic pyelonephritis, where the defect characteristic of renal tubular acidosis is merely part of a more generalised renal tubular functional deficiency. The primary cases are divided into the infantile type, first described by LIGHTWOOD,[37] with an onset in the first year of life, a high rate of recovery, and a preponderance of males; and the late primary cases, first described by ALBRIGHT et al.,[38] with an onset after the first year, a low recovery-rate, and a preponderance of females. Of altogether 162 cases 87 were of the infantile type and 68% of these were in males. Of the 75 late primary cases, 28 started between 2 and 11 years, and 47 between 15 and 60. Of all the patients 71% were female. Almost all patients in whom the disease started before the age of 18 months recovered completely, but none of the patients with later onset have been reported to lose their specific renal functional defect. There were interesting differences in the genetics of the two types of primary renal tubular acidosis. Among the 87 cases in the infantile group there were only 4 propositi with affected siblings, and their parents showed no evidence of the disease. In two of the families the parents were first cousins, and these workers therefore conclude that at least some of the infantile cases are due to a recessive hereditary factor. By contrast, of the 75 late primary type of renal tubular acidosis, 8 belonged to families in which the condition was passed from generation to generation—suggesting a dominant gene with varying and incomplete penetrance. The gene presumably has greater expressivity in females than in males. ELKINTON and his colleagues used the "clearance index" of hydrogen-ion excretion to diagnose subclinical renal tubular acidosis in an affected family. 3 children, apparently unaffected by the disease, were found to have a slight depression of the plasma-bicarbonate. 2 of these 3 children had a "clearance index" after ingestion of ammonium chloride which was either abnormally low or at the lower limit of normal. Renal tubular acidosis may be analogous to other hereditary biochemical diseases where the exact mode of inheritance becomes apparent only when more exact methods of diagnosis can be applied to the milder forms of the disease.

36. Pearse, A. G. E., Macpherson, C. R. *J. Path. Bact.* 1958, **75**, 69.
37. Lightwood, R. *Arch. Dis. Child.* 1935, **10**, 205.
38. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr., Roos, A. *Medicine*, 1946, **25**, 399.

Annotations

"LEVELS" OF ANÆSTHESIA

THE first scientific meeting to be held under the auspices of the Faculty of Anæsthetists of the Royal College of Surgeons in Ireland comprised a symposium on levels of anæsthesia. Such levels were originally defined, as Gilmartin [1] recalled, in relation to the clinical signs of ether anæsthesia.[2] The advent of the relaxant drugs finally made clear the futility of attempting a universal classification of levels; for with these drugs the degree of myoneural blockade must be assessed quite separately from the level of narcosis. Gray [3] explained that the so-called "signs of anæsthesia" can be caused in different ways, and only under certain well-defined conditions are they related to the level of narcosis. The concept of different levels of anæsthesia was further criticised by Wyke,[4] who presented a neurological analysis of the stages of anæsthesia. He regards the traditional concept of progressive dissolution of neurological function, from the cerebral cortex downwards, as based more on 19th-century theology than on 20th-century science. Anæsthesia, he suggests, is produced by pharmacological blockade of the polysynaptic relays—the reticular system often being even more susceptible than the cerebral cortex. The successive reflex changes of anæsthesia are therefore unrelated to hypothetical "levels of function" in the neuraxis. The words "level" and "depth" were clearly distasteful to many speakers, who preferred the term "stage of anæsthesia" which has a more dynamic connotation.

If we discard classifications of the stages of anæsthesia there remain (during spontaneous respiration) but three conditions—too deep, too light, and just right. The first of these conditions is characterised by undue depression of respiration and occasionally of blood-pressure. The second is characterised by reflex response to surgical stimulation; and the third by continued rhythmic respiration in the presence of the surgical stimulus. But the anæsthetist of today often finds assessment of the stage more difficult than did his predecessors. This is largely because he now employs agents which, of themselves, give a less clear indication of the level of narcosis than did ether. Mushin [5] has pointed out that the stimulus of strong ether vapour on the respiratory mucosa is probably greater than that of cutting the skin. Therefore the patient who inhales strong ether vapour with regular respiration is unlikely to respond to moderate surgical stimulation, and with attention to the breathing the patient is unlikely to become too lightly anæsthetised. Nevertheless, with ether, many patients are more deeply anæsthetised than the nature of the operation demands.

With the non-irritant inhalational anæsthetic agents in vogue today, anæsthesia may be maintained at a level no deeper than is required by the surgical stimulation; but the depth of anæsthesia can be gauged only by the degree of surgical stimulation, and reflex response can all too easily follow a sudden unexpected increase in stimulation. Sometimes matching narcosis with surgical stimulus may be difficult if not impossible. This difficulty may be circumvented by combining very light narcosis with

1. Gilmartin, T. J. *Irish J. med. Sci.* November, 1960, p. 490.
2. Guedel, A. E. Inhalational Anesthesia. New York, 1937.
3. Gray, T. C. *Irish J. med. Sci.* November, 1960, p. 499.
4. Wyke, B. D. *ibid.* p. 509.
5. Mushin, W. W. *in* General Anæsthesia (edited by F. T. Evans and T. C. Gray). London, 1960.

neuromuscular blockade sufficient to cause apnœa. This state necessitates artificial ventilation, which generally results in considerable reduction in the carbon-dioxide tension of the arterial blood. There is evidence that this contributes to the narcosis—probably by reducing the carbon-dioxide tension in the cells of the central nervous system. Under these circumstances the possibility of excessive narcosis may be excluded, and narcosis need be only deep enough to ensure that the patient is unaware of his surroundings. This is not easy since the cruder indications of consciousness are largely suppressed by the neuromuscular blockade. In practice the anæsthetist tends to rely on his drugs—assuming, for example, that the inhalation of 70% nitrous oxide will always cause loss of consciousness. This is unsatisfactory; and a device for detecting return of consciousness would be of value. Opinions differ as to the place of electroencephalography in routine monitoring of the level of consciousness. Although the appearance of the trace in light anæsthesia differs little from that in consciousness, changes induced by surgical stimulation or by opening the patient's eyes will often indicate whether the patient is conscious. A possibly more useful indication of unconsciousness is desynchronisation of the electrical activity over the occipital cortex with rhythmic photic stimulus.

Unconsciousness (defined as lack of awareness of environment) is not an essential feature of general anæsthesia. Anæsthetists have found that patients may be able to obey commands, and answer simple questions by signs, while adequately anæsthetised for major surgery; and the patient will usually have no recollection of the operation. Thus, not only is the traditional concept of "levels of anæsthesia" open to attack, but even the fundamental principles of narcosis for surgical intervention are no longer as clear today as they once appeared.

THALAMOTOMY FOR INTRACTABLE PAIN

THE development of techniques for causing small discrete lesions in the depth of the brain has made thalamotomy a practical proposition for the relief of intractable pain; and some preliminary reports came from France as early as 1949.[1] Mark et al.[2 3] have left electrodes implanted in the thalamus, in some cases for as long as nine months, making repeated electro-coagulation lesions when the clinical state called for this. They report on 17 patients, mainly with intractable pain from carcinoma. All but 2 had some relief of pain, though in some this was transient. Using the McPherson stereotactic instrument they placed lesions in the ventral posterior thalamic nuclei, the dorsomedial thalamus, and the brain-stem in the region of the third-nerve nucleus. The one necropsy they record, of a patient with an intended ventral posterior thalamic lesion, confirms the accuracy of their localisation. Because of the type of case treated, 8 necropsy studies are in fact available and will be published. This is of course essential evidence in any attempt to interpret thalamic function in terms either of the clinical changes noted after operation or of the findings from electrical stimulation or recordings from implanted electrodes, which Mark et al. also studied.

A simple clinical analysis of the results of these lesions reveals some interesting points. Clearly, long-continued relief of pain can sometimes be achieved without loss of appreciation of pin-prick and temperature change—at any rate in the head and neck regions, for in general Mark's results seem more successful in pain from the head and neck than from the trunk or limbs. It seems that lesions presumably in the thalamic region can commonly produce short-lived confusion. This observation, which has been noted, too, by workers operating on subcortical structures for the relief of parkinsonism, has important implications for the neurological substrate of normal mental function.

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2. Mark, V. H., Ervin, F. R., Hackett, T. P. *Arch. Neurol.* 1960, **3**, 351.
3. Ervin, F. R., Mark, V. H. *ibid.* p. 368.

ASYMPTOMATIC PAROTID ENLARGEMENT

BILATERAL enlargement of the parotid glands sufficient to distort the normal facial outline is not rare. In most cases the enlargement is due to inflammation, which is revealed clinically in pain and tenderness, and histologically in œdema and cellular infiltration. Usually such inflammatory enlargement is due to bacterial or viral infection. But severe cellular infiltration is not always associated with inflammation: gross enlargement due to intense infiltration is a recognised feature of several of the malignant lymphomas, especially lymphatic leukæmia; and a lymphofollicular type of infiltration is characteristic of the change in the gland in Sjögren's syndrome (kerato-conjunctivitis sicca), whose ætiology is unknown. In many patients with enlarged parotid glands, especially where there are no symptoms, the lesion cannot be attributed either to inflammation or to neoplasia. Such cases have been recognised for more than fifty years as being associated most commonly with either malnutrition or some disturbance of endocrine function; and in the past decade a clinical association between this form of parotid enlargement and Laennec's cirrhosis has been demonstrated.[1–3]

In an attempt to clarify the nature and cause of the parotid lesion in Laennec's cirrhosis, Borsanyi and Blanchard [4] studied 21 patients with this syndrome. In each case parotid-gland biopsy was undertaken, the resting salivary flow from Stensen's duct was measured, and the duct system of the gland was displayed by sialography. Histological examination clearly established that the increased size of the gland was due to hypertrophy of the secretory gland-cells associated with increase of their zymogen granules. Part of the overall enlargement of the gland was due to interstitial adipose tissue, and in some instances to moderate fibrosis. The increased spacing of both the interlobar and the interlobular ducts revealed in the sialograms was presumably the result of the acinar hyperplasia. Nevertheless, despite both the histological and radiological evidence of hyperplasia, no evidence of increased functional activity was obtained. Nor, on the other hand, was there any suggestion of functional impairment: resting salivary flow was within normal limits, and none of the patients complained of dryness of the mouth.

Evidently no firm conclusions can yet be drawn as to the nature and cause of the changes in the parotid glands associated with Laennec's cirrhosis. The absence of acinar destruction or inflammatory infiltration does, however, exclude direct action by some exogenous toxic agent that has escaped hepatic detoxication. The hyper-

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2. Rothbell, E. N., Duggan, J. J. *Amer. J. Med.* 1957, **22**, 367.
3. Wolfe, S. J., Summerskill, W. H. J., Davidson, C. S. *New Engl. J. Med.* 1957, **256**, 491.
4. Borsanyi, S., Blanchard, C. L. *J. Amer. med. Ass.* 1960, **174**, 20.

plastic changes suggest that some normal stimulus, probably hormonal, is reaching the gland in excessive quantity owing to impaired inactivation in the liver. This is the current explanation of the gynæcomastia in the closely similar circumstances of malnutrition and hepatic cirrhosis. There is strong evidence that such breast enlargement is produced by the excess of œstrogens resulting from reduced intrahepatic inactivation that has been demonstrated both in cirrhosis and in malnutrition.[5] No hormone can at present be blamed for parotid enlargement with such confidence as can the œstrogens for gynæcomastia. But the parotid enlargement in some patients with diabetes mellitus [6] provides some support for the view that disturbed hormonal activity is fundamentally responsible.

TOXOPLASMOSIS

TOXOPLASMA infection is believed to be very common; serological surveys indicate that by adult life a quarter to a half of the population of this country have been infected.[7] By contrast, illness due to toxoplasma appears to be rare; but there may be more of it than we think, and therefore reports of its varied manifestations are of value. Such a report has come from Glasgow.[8] It describes 11 congenital cases and 1 acquired case.

As in other series choroidoretinitis was the commonest sign in the congenital cases, being present in 8. Microphthalmos and intracranial calcification were found in 6; microcephaly and mental deficiency in 4; and hydrocephalus, hepatosplenomegaly, and neonatal purpura each in 3. Neonatal purpura is not as well known as the other manifestations, but it has been previously reported.[9–12] In 1 of the Glasgow cases it was ascribed retrospectively to toxoplasmosis after an accident, at the age of 11 months, which led to radiological examination and the demonstration of intracranial calcification. A dye test for toxoplasmosis showed antibodies present to the high titre of 1 : 1900. It was then remembered that at birth the baby had had severe neonatal purpura. Apart from the intracranial calcification, the only remaining sign of toxoplasmosis was microphthalmos of one eye. Surprisingly there was no choroidoretinitis. Choroidoretinitis is the commonest sign of congenital toxoplasmosis. It is not unlikely that in the majority of cases it is the only one, for it is estimated that in 25–35% of cases of choroidoretinitis the cause is toxoplasmosis. This sign may not be noticed till school age or even adult life; and diagnosis in individual cases may be difficult or impossible since antibody titres will have fallen to levels common in the general population.

The 1 acquired case in the Glasgow series was of a boy of 10 who had a swelling in his neck. Histological examination raised the differential diagnoses of lymphoblastoma, lymphosarcoma, or toxoplasmosis. High dye-test titres (1 : 640 rising to 1 : 2560) and complement-fixation titres (1 : 80 rising to 1 : 160) made the diagnosis of toxoplasmosis virtually certain, and this was supported by the favourable outcome. Although the Glasgow series includes only this single case of acquired glandular toxoplasmosis, such cases outnumber severe congenital illnesses. Many cases are so mild that they do not reach hospital, and the patients are treated, if at all, by the family doctor. In the very rare cases of severe acquired toxoplasmosis, predominating features have been meningoencephalitis, myocarditis, and pneumonitis; pericarditis, pleurisy, myositis, skin rashes, and liver and kidney damage have also been noted. In this country Potts and Williams [13] reported a fatal case of myocarditis in which toxoplasma was isolated from the heart. Although suggestive evidence, this was not conclusive; for the antibody titres were not high, and toxoplasma has been found in the heart-muscle of patients who died of unrelated causes. In a recent case in an adult,[14] six weeks of paroxysmal, dry cough was followed by bilateral pleurisy, basal pneumonitis, and pericarditis. A month later the patient seemed to be recovering but he died suddenly, apparently of pulmonary embolism. The subsequent finding of toxoplasma antibodies to the very high titres of 1 : 32,000 in the dye test and of 1 : 32 in the complement-fixation test in a specimen of serum taken during the illness made toxoplasmosis a highly probable diagnosis.

DUPUYTREN'S CONTRACTURE

ALTHOUGH Dupuytren's contracture was first described well over a hundred years ago,[15] and although it is by no means rare, remarkably little is known of its pathogenesis. As the standard treatment has for many years involved excision of the incapacitating sclerotic tissue, our ignorance cannot be attributed to lack of opportunity to examine the lesion.

In 1948 Skoog [16] showed quite clearly that the histological changes in Dupuytren's contracture were characteristic but varied with the stage of its evolution from an ill-defined richly cellular nodule of fibroblasts to a poorly cellular band of extremely dense fibrous tissue. He also called attention to the presence of collagen fibres that ended abruptly in the vicinity of the cellular nodules, and to fine grains of hæmosiderin within these nodules; and he regarded these two features as evidence that trauma was an important factor in the development of the disease.

In 1958 Larsen and Posch [17] reported a study of 61 surgically removed specimens of Dupuytren's contracture; and, although they identified hæmosiderin granules in 9 of them, evidence of rupture of collagen fibres was not obtained. An investigation by Larsen et al.[18] of a further 69 specimens, in which special care was taken in the orientation and sectioning of the specimens, has been more successful. Of the 69 specimens 45 were in the nodular stage of the disease, and of these 45 hæmosiderin was found in 19. Furthermore, several examples of abruptly terminating fibres were found in association with these nodules, together with others which passed uninterruptedly through them. These findings therefore strongly support Skoog's original contention that microrupture of the fibres of the palmar aponeurosis is an important factor in pathogenesis.

Larsen et al. attempted to confirm this hypothesis by reproducing the disease in 12 monkeys. Both the palmar

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6. John, H. J. *J. Amer. med. Ass.* 1933, **101**, 184.
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13. Potts, R. E., Williams, A. A. *ibid.* 1956, i, 483.
14. Ludlam, G. B. Personal communication.
15. Dupuytren, G. *Lancet*, 1834, ii, 222.
16. Skoog, T. *Acta chir. scand.* 1948, **96**, suppl. 139.
17. Larsen, R. D., Posch, J. L. *J. Bone Jt Surg.* 1958, **40A**, 773.
18. Larsen, R. D., Takagishi, N., Posch, J. L. *ibid.* 1960, **42A**, 993.

and plantar aponeuroses were used, and fibre rupture was produced by gentle traction in the long axis of the limb applied with hæmostats to a small portion of the fascia previously mobilised from its deep attachments. The affected tissues were removed for pathological study at intervals of two to nine months after the operation. Nodules visible to the naked eye were found exclusively at the sites of rupture. In the first two or three months they were soft and reddish grey but, they later became firmer and yellow grey as their vascularity decreased. Their microscopic appearance was virtually indistinguishable from that of the characteristic Dupuytren's nodules; and hæmosiderin, which was easily found in the first few months, had almost disappeared from the specimens removed after nine months. None of the animals, however, showed any clinical evidence of contracture.

In Dupuytren's contracture the absence of any convincing correlation between incidence and occupations in which relevant trauma is probable,[19] and the well-known tendency for the condition to recur after excision, suggest that the trauma itself is but the trigger and that the essential fault may lie in the way in which the patient reacts to such trauma. Many factors that can modify reactions to injury—hereditary, nutritional, and endocrine—are now known, and the essential defect in Dupuytren's contracture will presumably be found among them. This conclusion is somewhat strengthened by the frequency with which the disorder has been found in patients with alcoholic cirrhosis.[20]

VIRUSES AND CROUP

ACUTE laryngotracheobronchitis or croup is well known to those dealing with infectious disease in small children. Antibiotics have little influence on its course, and so it has been assumed that a virus may be the cause. This assumption is supported by the epidemiological finding that the older members of the family of a case often give a history of a recent cold or other minor respiratory infection. As techniques have improved, viruses have in fact been isolated from some cases. The nomenclature of these viruses was at first rather confused, but the following main virus types have been isolated: parainfluenza virus type 1 (also called HA2),[21] parainfluenza virus type 2 (also called CA and ALTB),[22–24] parainfluenza virus type 3 (HA1), influenza-Avirus, and in one study Echo virus type 11.[25]

Although these viruses were isolated from the respiratory secretions of affected children, they could have been there by accident. Echo-11 virus has been found in the fæces of healthy children and others with non-respiratory disease, and when it was given to volunteers the only respiratory symptom produced was sore throat.[26] Parainfluenza-2 virus has been found in the U.S.A.,[23] Canada,[22] and recently in England,[24] in the respiratory secretions of patients with croup; but the number of virus isolations has been small, and children without croup were not studied. Parainfluenza-1 (HA2) virus has been recovered from patients with croup and other respiratory disease, but not from matched controls.[21] This virus is known to produce diseases resembling colds or sometimes influenza in older children and adults.[27 28]

An extensive study of croup has been reported from an infectious-disease hospital near Melbourne.[29 30] Between May, 1959, and March, 1960, 237 cases were studied. Influenza-A2 and parainfluenza-3 viruses were found in the first two months. In the spring and summer parainfluenza 1 and 3 viruses were isolated in a few cases, but in the autumn parainfluenza-1 was recovered in over half the cases. In parallel studies parainfluenza virus was recovered from only "a minority" of cases of minor respiratory disease, and from 0·7% of 1369 "other patients". These findings indicate that parainfluenza-1 virus was associated with croup, but the association of the other two viruses with the disease is much less certain. Other observations suggested that parainfluenza-1 virus was also associated with pneumonia, but relatively much less frequently than with influenza. (This may have been because the parainfluenza virus attacked older patients less commonly than did influenza virus, rather than because the pathogenicity of the two viruses differed.) Another serological type of parainfluenza-1 virus, Sendai, apparently caused influenza in the Far East [31] and pulmonary disease in children in Japan [32] and Moscow.[33]

Gradually a picture of the causation of croup is emerging. Like aseptic meningitis or poliomyelitis it is produced by different viruses each of which usually causes various rather milder diseases. Those so far identified seem to be in the myxovirus (influenza-like virus) family. In any one season and any one place a particular virus may predominnate, as the Australian study has shown. Similarly, parainfluenza-2 virus was first isolated almost simultaneously in the U.S.A. and Canada and then disappeared for a few years. Influenza virus probably causes the disease mainly during influenza epidemics; but parainfluenza viruses 1 and 3 have been found almost the year round in Washington, D.C.

We probably still do not know all the viruses which can cause croup. Perhaps some of the recently discovered "Salisbury strain" viruses which usually cause colds in adults give rise to croup when they fall on suitable soil. When the newly discovered CCA virus [34 35] is about it is often to be found in infants with bronchiolitis but not in those with croup.[36] These diseases cannot be separated sharply on clinical grounds, but further work by the clinician and virologist should teach us much more about those complex interactions between the virus, the respiratory tract, and the environment which lead finally to that unique event—the individual case.

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Dr. T. A. LLOYD DAVIES has been appointed Senior Medical Inspector of Factories in succession to Dr. Sibyl Horner, who is retiring in the spring.

Special Articles

SPINAL INJURIES

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DURING the past twenty years there has been considerable improvement in the treatment of patients with spinal injuries. Before this, such injuries were customarily treated by what might be termed standard orthopædic measures—the fracture or dislocation was reduced either conservatively or by open operation; a plaster was applied, and the spine held in reduction for several months. The result was, at the best, considerable stiffness of the spine; at the worst, if the spinal injury was accompanied by paraplegia, there would be serious bedsores, urinary infection, urinary stones, gross contractures, and often, early death. Some rather more adventurous surgeons had practised laminectomies on spinal injuries with paraplegia; but, on the whole, results were disappointing.

The first great step forward in the treatment of spinal injuries was made by Guttmann (1947), who devised what may be termed the compensation method of treatment—that is, he ignored the spinal displacement, accepted whatever paralysis there was as inevitable and incurable, and concentrated on developing the body's power of compensation. He avoided reductions, operations, and plaster fixation; he concentrated on frequent turning to avoid bedsores, on intermittent catheterisation with strict aseptic precautions to avoid urinary infection, and on continued and repeated physiotherapy to avoid contractures. In addition, he stressed the importance of developing the arm and remaining trunk muscles; and he attached great importance to sport, occupation, and the patient's mental outlook. The results he achieved at Stoke Mandeville were a great improvement upon those usually obtained at that time, and his methods have become known throughout the world.

At almost the same time, Stanger (1947) was applying similar physiological methods to the treatment of spinal injuries complicated by paraplegia. He, too, accepted a certain amount of local deformity and concentrated on developing the spinal muscles and avoiding stiffness of adjacent joints. His results in the treatment of spinal injuries—mainly in miners—were a great advance on more orthodox methods; but, as was soon apparent, his methods of ignoring, so to speak, the spinal injury also had certain disadvantages.

Pathological Anatomy

Since the late war, largely owing to the work of Holdsworth (1953) and Nicoll (1948), we have entered on the modern phase of discrimination in treatment, based on the fundamental concept that certain spinal injuries are stable and others unstable. The concept has been further clarified by recent laboratory work performed by Roaf (1959). The classical descriptions of most spinal injuries attributed them all to flexion forces, and classified them all as fracture-dislocations. Barnes (1948) pointed out that certain neck injuries were due, not to a flexion force, but to an extension injury, and the concept of a hyperextension injury arose. Later, Holdsworth (1953) pointed out that a rotation force was important in producing tearing of interspinous ligaments and dislocations (figs. 1 and 2). Since then, further experimental work has shown that a flexion force by itself cannot rupture interspinous ligaments and always causes vertebral-body compression (figs. 3–7). Similarly, a pure extension force is unlikely to cause rupture of the anterior longitudinal ligament; a compression fracture of the vertebral arch is usually produced. If, however, a rotation force is applied with the spine slightly flexed, the interspinous ligaments are very easily torn. Dislocation of the cervical spine can

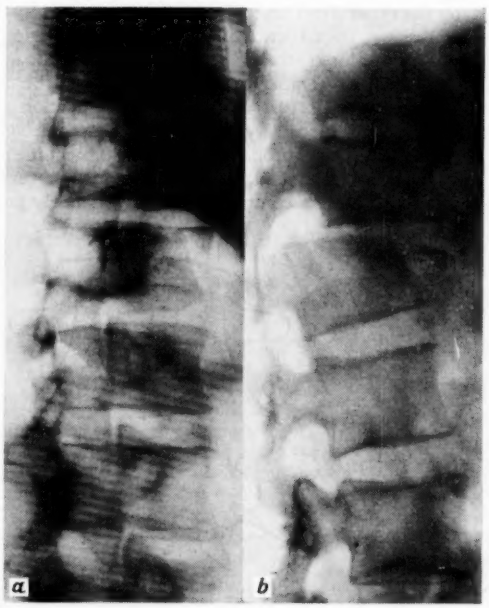

Fig. 1—(*a*) Anteroposterior view and (*b*) lateral view of fracture-dislocation from rotation injury. Unstable; complete paraplegia.

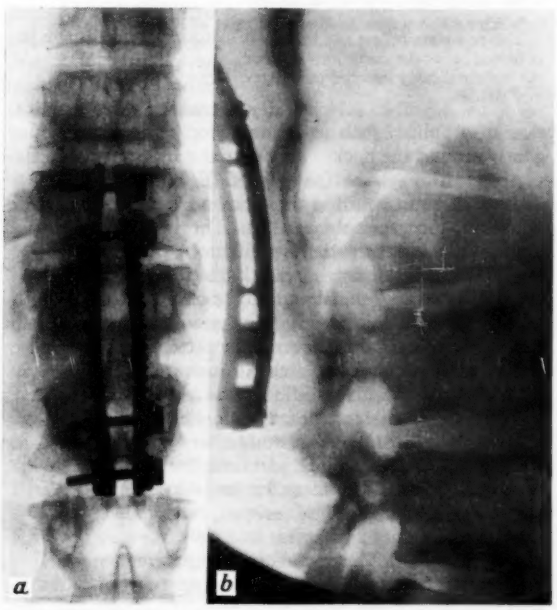

Fig. 2—(*a*) Anteroposterior view and (*b*) lateral view of same patient after reduction and plating, which was followed by excellent neurological recovery.

be produced by relatively slight manual pressure—a fact which appears to have been known to the traditional garrotters of medieval Europe and Asia. Similarly, if a rotation force is applied to the extended spine, it will produce tearing of the anterior longitudinal ligament. If, therefore, the deforming force is mainly rotational, a dislocation or fracture-dislocation of the spine is likely to result (fig. 8). This is always an unstable injury, and in some cases patients who had no paralysis at first have later become paralysed because of further displacement of these unstable fracture-dislocations. Similarly, in some cases patients have made good neurological recoveries after correction and fixation of such unstable fracture-dislocations (figs. 1 and 2).

Treatment

First-aid

If the patient is unconscious from an associated head injury, the usual measures to maintain a clear airway and to avoid aspiration of blood, mucus, and vomit are all-important: the patient should be placed on his side and the jaw held forward. As head injuries and cervical-spine injuries are often associated, unnecessary movements and especially twisting of the neck, should be avoided. If the patient is conscious but paralysed, he may have respiratory distress and this requires primary consideration. But, if possible, any patient with a suspected neck injury should have the neck lightly supported, either by gentle manual traction or by application of a splint, such as a long woollen scarf wrapped gently around the neck. Any extreme movement, particularly twisting, should be avoided (fig. 9).

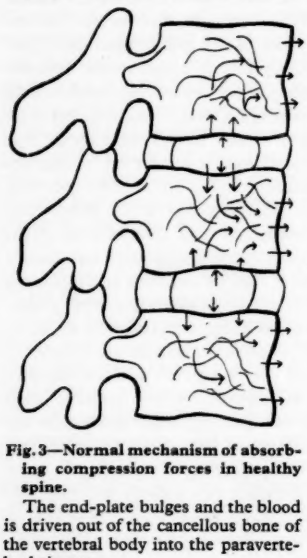

Fig. 3—Normal mechanism of absorbing compression forces in healthy spine.

The end-plate bulges and the blood is driven out of the cancellous bone of the vertebral body into the paravertebral sinuses.

Stable fractures in the thoracic and lumbar regions do not require any special measures. There is no point in placing the patient in the prone position. This may, indeed, cause harm if there are associated abdominal and thoracic injuries or, in unstable injuries, if there are locked facets. Simple recumbency on a firm stretcher is all that is required for stable injuries; but, as it is often difficult to differentiate between stable and unstable injuries, all spinal injuries should be considered unstable until the patient has reached hospital and been X-rayed. The ideal first-aid treatment for unstable fractures is gentle longitudinal traction; but, at all costs, unnecessary movement and twisting of the spine should be avoided. The patient should be gently rolled on to a firm stretcher and then laid supine, and gentle manual traction applied to his legs. He must never be lifted by shoulders and knees—that is, with his back unsupported. As soon as possible, he should be taken to a hospital with good radiographic facilities, and with nurses and doctors who are accustomed to such injuries. If the patient is paraplegic, pressure on the legs and buttocks should be avoided. Boots, shoes, and tight clothing should be removed; hard objects, such as keys, should be taken out of the pockets, and the legs rested on pillows (fig. 10).

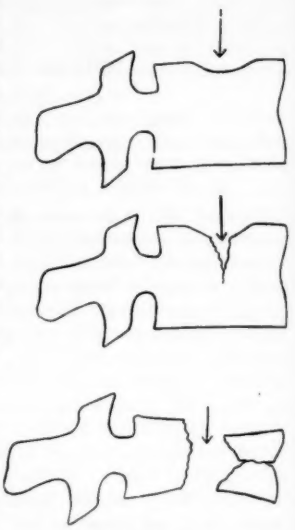

Fig. 4—Three degrees of compression fracture of the vertebral body with healthy disc and nucleus pulposus.

Definitive Treatment

The correct treatment is based on accurate diagnosis and differentiation between stable and unstable fractures. This requires careful clinical and radiological examination. Pronounced tenderness and local bruising over the spinous processes with separation and malalignment of the spinous processes indicate an unstable fracture-dislocation.

The modern treatment of an unstable fracture-dislocation of the spine from a rotation force is reduction by open operation, and retention in the reduced position—usually by applying plates to the spine. This gives the best possible chance of recovery to the spinal cord and its roots. With an incomplete lesion—for example, where there is some sensory sparing—considerable and worthwhile motor and sensory recovery can be expected (fig. 2).

If, on the other hand, the deforming force is mainly one of compression, then there will be little or no tearing of interspinous and intervertebral ligaments; the spine is, in fact, stable (fig. 4). Under those circumstances, the only treatment required is rest in bed. Plaster-fixation and plating are both unnecessary and harmful. Laminectomy is also harmful as it will probably convert a stable spine into an unstable one. In general, the prognosis for recovery of the spinal cord after a compression injury is fairly good,

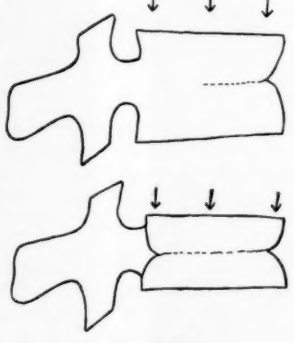

Fig. 5.

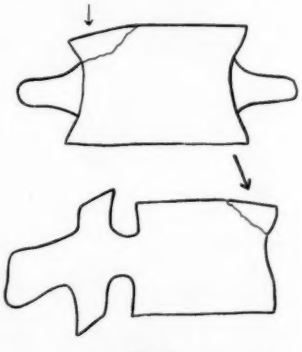

Fig. 6.

Fig. 5—Two degrees of compression fracture of the vertebral body, where the nucleus pulposus is not functioning and force is transmitted through the annulus.

Fig. 6—Lateral and anterior marginal fractures due to compression.

apart from the severe multiple crush injuries of the cervical spines of motor-cyclists who wear crash helmets. This accounts for some of the successes claimed in the past for procedures such as laminectomy—the cord would probably have recovered anyway. Of course, if there has been severe pulping of one or more cervical vertebræ, irreparable damage will have been done to the spinal cord; and the prognosis for recovery can be estimated from the amount of comminution, the amount of spreading of the fragments of the vertebral body, and the magnitude of the force. A considerable series of postmortem studies on such patients has confirmed that, in general, the major part of the damage to the spinal cord is done at the moment of injury. In thoracolumbar and lumbar compression fractures, however, there may be a place for late laminectomy—that is, after four or five weeks when the risk of rendering the spine unstable has passed. If the lesion is incomplete but is not improving, myelography is usually undertaken. If there is a spinal block but there is still a possibility of some of the non-conducting spinal tracts being in continuity, a laminectomy will give them the best chance of recovery. This is especially true where the lesion is partial.

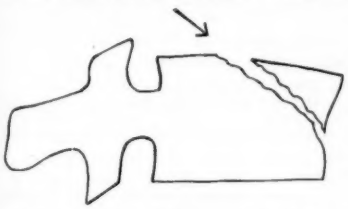

Fig. 7—Compression fracture due to oblique compression force.

It might be thought that I have paid insufficient attention to the syndrome of massive disc prolapse as a cause of paraplegia. In point of fact, massive disc prolapse rarely, if ever, occurs as a complication of injury to a healthy spine. Numerous experiments have shown that, if a healthy spine is compressed, the vertebral body always fractures before the disc ruptures; and any disc prolapse is only secondary to a general comminution of the vertebral body. The massive disc-prolapse syndrome always takes place in a patient whose disc is already abnormal. There is, therefore, nearly always a history of preceding back trouble. In addition, the precipitating injury is usually trivial and the onset is subacute—pain is followed by progressive weakness of the legs. Radiographic and myelographic findings are usually typical, and this syndrome need seldom be confused with a true spinal injury.

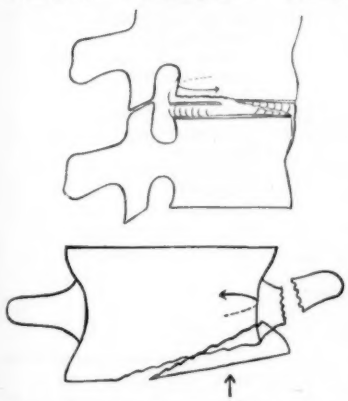

Fig. 8—Lateral and anteroposterior view of rotation fracture-dislocation.

An unstable fracture associated with extensive tearing of the interspinous ligaments.

Paraplegia

The techniques instituted by Guttmann for treatment of the paraplegic are followed in most parts of the world; but there have been several recent advances in the treatment of spasticity. In particular, it has become realised more and more that spasticity interferes gravely with rehabilitation, and that the patient with flaccid, though completely paralysed, legs finds it far easier to move about, dress himself, "walk", get in and out of a chair, bath, &c., than one whose legs are spastic, even though they may retain a flicker of voluntary movement. Spasticity may be relieved either by intrathecal injections of phenol (Nathan 1959) or by peripheral operations. Intrathecal injections of phenol have the slight disadvantage that they may upset bladder function, if this is at all precarious. They are certainly the method of choice if the bladder is already paralysed. If, however, it is felt that the risk of interfering with bladder function is too great, then spasticity can be notably relieved by a series of peripheral operations—namely, intra-abdominal extraperitoneal division of the obturator nerve and iliopsoas muscle,

Fig. 9—Wrong way to lift patient with spinal injury.

Cervical spine and thoracolumbar region unsupported and liable to further displacement.

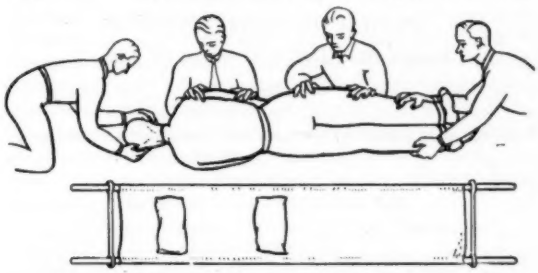

Fig. 10—Right way to lift patient with spinal injury.

The patient is rolled on to a firm stretcher, with gentle longitudinal traction on head and legs.

division of the hamstring muscles with sliding down of the gastrocnemius, and, if necessary, division of the tendo Achillis.

Finally, there have been considerable advances in the treatment of irrecoverable tetraplegia with paralysis after severe cervical injuries. With the increasing speed of motor vehicles, and the more frequent wearing of crash helmets by motor-cyclists, the frequency of such injuries is increasing. In the early stages, the patients are likely to die from respiratory embarrassment, but a timely tracheostomy and the use of a Tunnicliffe jacket respirator will save most of them. Another early complication is intestinal ileus; gastric suction and intravenous fluids will tide most patients over this complication. Provided they survive the early stages, and provided bedsores and urinary infection are avoided, the prognosis for life in tetraplegics is good. I have had a number of patients who have lived healthy lives for several years despite complete paralysis from the 6th or 7th cervical segment downwards.

If there is complete transection of the spinal cord, excessive local treatment to the spine is not only unnecessary but positively harmful, and will make nursing a great deal harder. Procedures such as laminectomy, open reduction and wiring, or skull traction do not help a com-

pletely transected spinal cord to recover. If, therefore, the tetraplegia follows either a severe crushing injury or a double fracture-dislocation—that is, both facets are dislocated—the only treatment required for the neck is recumbency with whatever minimal splinting is required for comfort.

Where the 7th cervical root has been spared, the patients can extend their elbows and wrists and have sensation in the all-important thumb and index-finger area. They can be taught to perform a very considerable number of simple movements, either bimanually or by means of an appliance —e.g., they can write, feed themselves, and turn the pages of a book. In selected cases, arthrodesis of the thumb in a position of function and a tenodesis of the flexor tendons to the index and middle fingers will restore a useful power of pinch; and sometimes such patients have even been taught to change their own catheters. An important part of the management of patients with tetraplegia is to ensure that they can shift their position, turn from side to side, and spend as much time as possible in a chair rather than lying in bed. In order that this can be done at home, various mechanical hoists have been devised; and it is now possible for a small woman, unaided, to look after her sixteen-stone husband, although he is paralysed from the 6th cervical segment downwards. In the treatment of all tetraplegics and paraplegics, suitable occupation of the patient's mind is all-important.

Summary

In general, spinal injuries are of two types—compression and rotation. After a compression injury the vertebral body collapses but no ligaments are torn, the spine is stable and the only treatment usually needed is rest in bed. Operation is contraindicated. After a rotation injury the spine is unstable, and operative reduction and fixation are usually indicated.

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Medical Education

A POSTGRADUATE PUBLIC-HEALTH COURSE

From the Students' Point of View *

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"... In short, no one would admit that he could not see these much admired clothes; because, in doing so, he would have declared himself either a simpleton or unfit for his office. ... 'But the Emperor has nothing on at all!' said a little child."—HANS ANDERSEN, *The Emperor's New Clothes.*

PUBLIC-HEALTH specialisation differs from most other medical specialisation. Most specialists receive their training by working for a number of years in a hospital or some other medical institution: they earn their living while they do so, and often they can train for a specialty even in small and remote regions. In contrast, the doctor specialising in public health undertakes a year's study during which his role is passive and he is usually unable to earn his living; and, as such courses are relatively few, he often has to travel far from his usual place of work.

Considerable efforts are made by Governments and by international bodies to accelerate the advance of public health by enabling doctors to specialise in it. How far do these efforts succeed?

Discussion of public-health specialisation [1–4] is usually from the instructor's point of view [1 2 4]; but the opinions of "instructees" may also be useful, particularly where previous work in public health has given them some definite ideas about their needs. Having had such experience and having recently gone through such a course, we think it may be worth describing some aspects of the instruction which look problematical to the student.

THE COURSE

Curriculum, Methods of Instruction, and Organisation

The course was for the diploma in public health conforming to the official English requirements—i.e., the General Medical Council regulations. The curriculum consisted of some 40 items (table I).

A total of approximately 600 instruction periods was provided (i.e., instruction-time units of 40–60 minutes

TABLE I—THE CURRICULUM: THE SUBJECTS AND THE TIME ALLOCATED TO THEM (HOURS) [c a]

Biostatistics[e]	50	Radiation	5
Bacteriology[b]	42	Care of handicapped	4
Physiology[b]	42	Health education[d]	4
Public health	31	Planning & administration	3
Epidemiology	30	New towns	3
Child heath	18	Geriatrics	3
Environmental hygiene	17	Sociology	3
Psychology	16	Veterinary surgery	2
Entomology[b]	16	Town planning	2
Nutrition	16	International health	2
Various (introductions, libraries, &c.)	10	Family planning	2
Occupational health	10	Growth and development	2
Social security	10	General practice	2
Mental health	10	Dental health	2
Sanitation chemistry	9	Childhood accidents	2
Genetics	7	Venereal diseases	2
Tropical health	6	Port health	2
Protozoology[b]	6	Architecture and public health	2
Helminthology[b]	6	Tuberculosis	1

TUTORIALS 40 ELECTIVE SUBJECTS 40

VISITS: Fever hospitals 12 visits[f]
Other hospitals 4 visits[f]
Others 8 visits[g]
Local-authority public health 16 visits[f]

a. Because of some deviations between the programme and the actual course there may be a few small inaccuracies in the figures.
b. Including demonstrations.
c. Some instruction hours were called symposia; in practice, these were lectures given by a number of lecturers.
d. A one-day seminar.
e. Including class exercises.
f. Half-day visits (about 2 hours).
g. Some half-day and some whole-day visits

* While doing this work, one of us (J. Cohen) was on a W.H.O. fellowship. The views expressed are not necessarily those of W.H.O. The other (A. M. Robertson) participates with the permission of Dr. H. M. Archibald, principal medical officer, Ministry of Health, Kaduna, Northern Nigeria.

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each). Four-fifths of these periods were received in the institution; the remainder consisted of visits to places of public-health interest.

The methods employed were:

Lectures	58%	of instruction time
Demonstrations	10%	" "
Private study	10%	" "
Tutorials	8%	" "
Practicals	7%	" "
Elective subject	7%	" "

Instruction at visits, which made up a fifth of the instruction time, usually again took the form of a lecture with some demonstration following (of patients, apparatus, organisation, &c.).

For the tutorials the students were allocated in groups of 10–12 per tutor, and the work consisted in making a small field inquiry under the tutor's guidance, the subject and methods being more or less fixed by the tutor.

The elective subject gave the student an opportunity to study one subject (out of a choice of seven) in more detail than it was taught in the general course.

Apart from one solitary seminar, two additional forms of instruction were employed. Each student prepared a daybook and a dissertation. In the former he recorded a limited number of critical comments on visits and matters of current public-health interest. The latter was a study of an approved subject in which the student had special interest or experience.

Attendance at all the items of this instruction was obligatory, and was confirmed by signing one's name in an attendance register twice a day.

The lectures at the institution were given to the whole class. For the visits, the tutorials, and the elective subjects, the class was divided into groups varying, according to purpose, from 10 to 20 members per group.

TABLE II—EXAMPLES OF DAILY TIMETABLES (NOT INCLUDING TRAVEL TIMES)

Day A		*Day B*	
10.00–11.00	Lecture	10.00–12.30	Visit
11.00–11.30	Break	—	
11.30–12.30	Lecture	—	
12.30–14.00	Break	—	
14.00–15.00	Lecture	14.00–15.00	Lecture
15.00–15.30	Break	15.00–15.15	Break
15.30–16.30	Lecture	15.15–16.15	Lecture

The instruction was given Monday to Friday; the periods, usually four a day, were spread between 10 A.M. and 5 P.M. Two typical days' programmes are shown in table II.

The Teachers

The instruction at the institution was given by nearly seventy different lecturers, besides the many lecturers, assistants, technicians, and others, lecturing and guiding at the visits. Of the lecturers at the institution, about a tenth belonged to the staff of the public-health department, two-fifths were from other departments (statistics, physiology, &c.), and almost half were external lecturers. Three individual lecturers gave 20–25 lectures each, nine gave 11–20, and sixteen gave 3–10, the remaining forty giving 1–2 lectures each.

The Students

The class consisted of about 60 students. Some 40% were foreigners from Europe, Asia, South America, and Africa, while those of English origin had been working, before the course, in the Armed Forces (17%), in the Overseas Civil Service (13%), in hospitals and research (9%), for English local authorities (7%), or in miscellaneous occupations. The majority, both foreign and English, had worked previously in public health, this experience ranging from very little to 1–2 decades. The average age of the students was approximately 35.

DISCUSSION

Scientific evaluation of such a course would require a measurement of the " added values " acquired by the participating doctors (i.e., their increment in useful knowledge and faculty of judgment), an estimate of the effect of this increment on their work in future years, and a weighing of these " gains " against the " price "—i.e., the efforts made by the doctors to go through the course, the discomfort involved for them and their families, the disturbance arising in their regular place of work through their absence for a year from their post, and the expenses incurred whether by themselves or by the public bodies granting stipends or financing the teaching institutions. Whether satisfactory methods for such a survey have yet been elaborated seems doubtful. But in the absence of objective measurement, individual opinions may be of some value in furthering the evolution of public-health specialisation. And, while the opinions stated here are our own, talks and discussions with colleagues, and with some of the lecturers, show that many of them are shared.

The peculiarity of public-health postgraduate training, compared with other medical branches, is probably to be explained more by its historical development and its statutory standing than by the content of public health. One may fairly ask whether some of its features—its being school-like, its brevity, its lack of practical in-training—are justified and whether they do not contribute to a lower status and standard of this branch of medicine and bring about an undesirable selection of candidates going into this specialty.

The Curriculum

The English courses for the diploma in public health are mainly planned to meet the requirements of the General Medical Council. These requirements were originally laid down some decades ago for doctors intending to enter English local-authority public-health work, and, though there have been revisions from time to time, they have tended to lag far behind practice.[1]

Much of the material (e.g., in bacteriology, physiology, nutrition, and child health) is nowadays incorporated in the general medical curriculum: the average doctor has already learnt these subjects, and while he has forgotten much of the factual detail, as is the fate of such knowledge which is not in daily use, he has an understanding of the principles. The doctor working in public health likewise uses the detailed facts but seldom; when a need for them arises, the data he learned (as an undergraduate or postgraduate) will be forgotten or outdated, and only the knowledge of the principles will guide him to the information he needs from up-to-date books or from a specialist in the subject.

Though such matters are important for the understanding of certain public-health activities, we may ask whether repeated memorisation of much detail is really useful. This is questionable even for the doctor intending to work in English local public-health services, for whom the courses were originally designed; and it is even more questionable now that most doctors specialising in public health do not belong to this class and have different needs.

The number of subjects of importance for public health grows (radiation, sociology, health education, and others),

and some of the newer ones are as important as the earlier ones (such as bacteriology and chemistry). The wish not to neglect any of them leads to a large number of topics being dealt with superficially; and there is more and more risk that the presentation of the concept of public health as a unity will be lost.

Apart from this "natural" increase in subjects, there was in this course an artificial splitting of defined subjects into subsubjects, every one of these treated by another lecturer supposed to be a subspecialist (or superspecialist?). In this way the coherence of these subjects is lost, while the alleged advantage of having them presented by a specialist cannot be realised because there is no time for serious discussion. It is also difficult to coordinate the different lecturers; some topics are repeated, because each lecturer feels that they belong to his subsubject, while others remain unmentioned because every lecturer is confident that somebody else deals with them.

The Method

Instructing mainly by obligatory lectures, where the students are supposed to make detailed notes for recapitulation, has a number of disadvantages. It gives the student a passive part in the process of learning, whereas contemporary trends lay stress on active learning, which stimulates more interest, ensures a better understanding, and directs the student to continue studying after departing from the school or course. This question of active versus passive learning is the more important for the student who is an adult—a postgraduate—and who may have already worked for some years and be accustomed to an active, sometimes even rather independent, occupation. Such people—and this public-health course was to a large extent composed of them—find it difficult to be reduced to passive listening for many months. Again, such a uniform method takes no account of differences in individual optimal perception (visual or acoustic) or in individual habits of learning, which are likely to be quite pronounced in people of these ages and experience. It is also little adaptable to the wide range of needs and interests to be found among doctors with varying experience of the diverse branches and circumstances of public health, and it makes no use of this potential of different experience to enrich the instruction through interchange of knowledge between such students. Obligatory attendance at lectures is only doubtfully justified for undergraduate university students, and for postgraduates we cannot see how it is justified at all.

The course's intimate connection with the General Medical Council rules also affects the instruction, which is very much orientated towards the statutory examinations. The teachers are from the start examination-minded, and soon the students become so too. No longer is it the intrinsic value of a subject which fixes the attention, but mainly the weight it may have in the examination.

It seems questionable whether the present requirement of a rather lengthy dissertation (5000–25,000 words) is the best devisable exercise of this kind or whether a series of shorter reports on a number of subjects would not be preferable. The daybook is an exercise of some usefulness, but the fact that the comments in it are not discussed with the student detracts from its value.

The Organisation

Though the number of instruction hours was not excessive, averaging 4 a day, most of the day was covered by this amount of instruction. This was brought about by the spacing of the hours (table II). The actual instruction times may have been 4×50 minutes $= 3^1/_3$ hours a day, but the student was bound to it for $6^1/_2$–7 hours, without being able to make much use of the breaks; these were rather long as rest pauses but too short for concentration on some intermediate study. In addition to this, the time the student spent on travel often amounted to 1–2 hours a day, so that a whole working day of 8–9 hours was used for an actual instruction time of $3^1/_3$ hours and the student might be left with an acute sense of frustration. This sense of wasted time was enhanced when 3 or 4 hours of travel were spent on visiting an institution for 1 or $1^1/_2$ hours, where the instruction consisted again mainly of a lecture—the more so when the subject and its level of presentation were not what he expected.

The Teachers

Though not less important than curriculum and method, the quality of teaching (audibility and liveliness, intellectual clarity, and logical construction) is a delicate topic. Obviously, on a worthy subject, a lecture, a seminar, or a discussion can be highly stimulating or informative, or it can be just very boring. Still, these qualities are extremely difficult to measure fairly and adequately, and different observers may differ widely in their evaluations. Our own impression—necessarily subjective, but shared by other colleagues—was that this aspect of teaching was often neglected. In public health as elsewhere in academic teaching, little regard is usually paid to the teaching ability of the instructors. In a postgraduate course in which the instruction is given mainly through lectures, this defect is bound to create rather trying situations.

The Students

Public health today is a very wide and branched subject; and its priorities differ from country to country. Doctors coming for a year's study in it vary widely in their previous experience, some having worked in public health for years while others are entering it for the first time; and they vary no less in the kind of future jobs they are looking forward to. They differ, therefore, both in interests and in their needs for detailed knowledge. Is it practically possible to bring all these under the roof of one rigidly defined course? The answer seems to be in the negative.

SOME POSSIBLE CHANGES

Definite conclusions or suggestions cannot be expected from so limited and deliberately one-sided a description. Yet some possible lines of change emerge, which partly follow the trends of earlier proposals.[1 2]

One way of change would be an adaptation of the present courses by making both their curriculum and their methods more flexible. The curriculum could be built up from a small number of basic subjects (e.g., evolution of public health in different countries, social services related to public health, statistics and epidemiology, administration), which would be obligatory and common to the whole class of doctors specialising in public health, together with a larger number of other specialised subjects (e.g., sanitation, nutrition, bacteriology, mental health, radiation) from which each student would select a certain minimal number according to his needs and interests. This would allow more profound study of each subject, would give a sense of achievement and intellectual satisfaction, and would discourage the use of fleeting superficial notions. The student would thus be trained in the principle and method of a serious approach, which he could apply in his future career.

In the instruction of postgraduate adults, methods of instruction should be less rigid. Whether a person prefers to acquire the necessary knowledge by attending a lecture, by reading a textbook, or by going through periodicals should be left to his own discretion. It may be useful, however, to encourage work in discussion groups where every member undertakes to study an aspect or chapter of a subject and report on it to the group. Through these groups contact and discussion can be promoted with the other classes of public-health workers, engineers, nurses, social workers, &c., as a preparation for teamwork with these professions in the future.

Visits can be an essential part of the instruction. But, wherever possible, the student should have a chance to observe the actual working of the service or institution, and the visits should be so arranged as to keep the ratio " travel time to study time " as small as manageable.

More attention should be devoted to the quality of teaching. Members of the staff of public-health institutions for whom instruction is a major function should be qualified to perform this function and should regard teaching as a no less important part of their work than research.

Another possible way of change would be to make preparation for this specialty more like preparation for other medical specialties. The doctor specialising in public health would have to work for several years in certain recognised public-health formations (e.g., local-authority public-health departments, industrial health services, mother and child welfare clinics, rural health units), as in practice he frequently does today; and this would be analogous to the hospital or outpatient-department work of doctors specialising in other fields. In this defined period of in-service training could be intercalated small periods of guiding formal instruction at some larger centre—i.e., a university with a well-developed public-health or social-medicine department. The necessary theoretical knowledge could be defined and form the matter of an examination after the required field work.

In putting forward these lines of change, no attention has been paid to the statutory rules governing the study required for the careers of a limited group of public-health students. We are here regarding public health as a real university subject (i.e., a science and a method which has general principles): if there are to be statutory rules, they should be governed by public-health needs and not inversely. Finally, to quote Grundy and Mackintosh,[1] " it is of the utmost importance that teaching should not lag behind practice but anticipate the needs."

SUMMARY

A postgraduate course in public health is described and its relation to the needs, interests, and expectations of contemporary students is discussed.

The curriculum seems to lag behind the widening scope of public health and to be very much orientated to technical details of English local-authority practice. It tends to include a little bit of more and more subjects and does not allow students to choose these according to their different backgrounds and needs.

The main method of instruction is by lectures; this does not accustom the student to active thought and independent study. Most instructors lack training in teaching, and the quality of instruction is very variable.

Possible lines of change seem to be either (1) to introduce more flexibility into the curriculum and methods of the present courses, or (2) to bring public-health specialisation into line with other medical specialisation by making the training an " in-service " one, where the student learns while working under supervision of experienced specialists.

The Widdicombe File

LXVIII.—PRIVATE PRACTICE

DEAR SIR DANIEL,

You may remember a brief conversation we had some time ago, and that I promised to write to you later, giving some of my views. Like all matters of opinion, they may be valid only for the person who holds them. Actually, I don't expect many of your group to understand them, let alone agree with them, but you may be interested to know where I stand.

First of all, let me say that I personally owe a great deal to private practice. You may remember that my father did nothing else, and without it I should have had no medical education. State Medicine filled him with alarm and disgust, because the work he did was peculiar to himself, and in his field few could equal and none surpass him. Possibly because my work is less original, less thoughtful, less difficult to define or categorise, I find it easier to fit into a pigeonhole. I find in hospital work a continuing satisfaction, where he outgrew the bounds it sets.

When at last a consultant post came my way, various commitments made it seem essential to do private practice, and I tried hard to make it work, and make myself believe I liked it. Judging from the returns, it would have been very remunerative. Why, then, give it up? Am I not (as so many people say) making a very big mistake?

First, there were the difficulties of deciding who was a genuine private patient. Some people like to pay for services, and willingly pay for treatment, appliances, drugs, and so forth. Many business and professional people become private patients for the sake of having separate rooms, with telephones, and with more liberal visiting-hours. A few are used to buying what, or whom, they want, in any case. For all those there is no problem.

The difficulty arises with those who ring up because Mrs. So-and-so advised them. They haven't seen their family doctor, and often come without his knowledge or approval. Then there are those who understandably tire of outpatient queues and ask for private appointments. A former chief taught me never to see such people, and I am convinced he was right. The third group finds that it takes six weeks to get an outpatient appointment, but only six days for a private one. From their point of view, it must seem quite reasonable to pay the price. From mine, it is impossible to avoid the conclusion that this is barely disguised bribery: " If I go to hospital, I can't see the doctor for a month. If I give him five guineas, he'll see me to-morrow." (Please understand that this is just my way of looking at it. Many colleagues, for whom I have great respect, see it differently.)

Secondly, I dislike being bought. If one has a saleable commodity, whether it be a car, a piece of cheese, a service, or an opinion, one may expect a fair market price. It wasn't people buying my opinion that irked me, but their trying to buy me as well. I'm no good at dancing attendance on folk for what I can get out of them. If

they're ill, I'll come at any hour of day or night; but if they're not ill, my time is better spent.

Then I'm so hopeless at business. I don't like sending accounts to people for making them better, let alone for making them worse, or to their executors for killing them. If I had liked making out bills, I'd have become a grocer. I would much rather deal with the patient as I see fit, and get my money in salary from another source. You may say that this is an easy way out and absolves me from responsibility that more dedicated men do not shirk; but I do see the patient, not his pocket.

Again, it lets me out of the rat-race. There isn't a big one in our town, but I've seen it in London and abroad, and it can become ruthless and demoralising. It tends to involve the wives and families as well.

Instead of having to rush about with a constant temptation to skimp, I can pay attention to what I believe to be my proper work. What time is left over can go to reading or to a clinical project, satisfying to me, and possibly ultimately of value to the community.

Some people claim I'm depriving worthy patients of my services. I have enough insight to know that I am no cleverer than the rest, and few people will go wrong for lack of my help. There are plenty of men left in my line of work to cope with the ones who like to pay.

" You owe it to your family to earn more," you may say. At one stage that seemed true. However, if one gets in at 10 P.M., not having seen the children for days, and having hardly spoken to one's wife, it doesn't take long to realise that what is gained on the roundabouts is lost on the swings. Why earn thousands, to send the children to expensive schools, if it means that you become strangers to each other? A family is a unit, at least ours is, and while we talk of bringing up the children, they equally certainly mould our opinions and behaviour.

Having spent years as registrar and senior registrar I find that the necessity to watch the budget presents only an old and familiar problem, which we solved long ago. The problem of prospective affluence was far worse and threatened to become dangerous. The golden calf can demand many sacrifices, some human.

I think you believe that private work provides an incentive to good practice, and enables the specialist to keep up a high standard in public practice. At one time I thought this, but in my own experience it has not proved true.

Whether to remain on a part-time contract or to change to whole-time raises a problem, but for the moment the part-time man seems to have a slight advantage, and at least on paper retains some freedom of action.

You know me well enough, I think, to understand that I'm not talking from any doctrinaire viewpoint, and that what I say is my own opinion. Nobody else need share it, many will disagree with it, some (as I say) won't even understand it. For me—possibly for me alone—private practice is incompatible with *æquanimitas*. The experiment has been tried, the evidence has been collected, and the conclusion logically reached, by the Hunterian method.

We've also discovered that this is an effective if expensive way of stopping the telephone ringing!

With kindest regards to Lady Whiddon and yourself.

Yours sincerely,

ROBERT HEWER.

In England Now

A Running Commentary by Peripatetic Correspondents

IT is well known that a top executive is a man who can take three hours off for lunch without any effect on production at all. The corollary of this is also quite well known, that a lot of useful business can be done over lunch, including, of course, the appointing (or anyway vetting for appointment) of top executives. Doctors don't as a rule become top executives, but occasionally some business needs a medical adviser, and the process of vetting is apparently much the same. This is all part of the daily life for business, but quite an experience for any doctor who wasn't born with his W.1 address printed on his visiting card and who isn't wholly intimate with those jolly little hotels in Park Lane. Forewarned is forearmed, and a little thought about technique may not come amiss.

First, the aperitif. This takes from 12.45 P.M. till 2 P.M. Don't plead for a small one; this is a premature and probably fatal admission of weakness. Don't stand out for a soft drink and thereby reveal great moral character but nothing else at all: you haven't been asked to lunch as a potential adviser on Virtue. The best ploy is to err on the large side, sip the air above it periodically and don't let it get empty enough to be refilled before 1.30 P.M. After that it is safe enough to accept one small one, as you will be assumed to have got round two or three large ones already and your modesty in not taking a fourth may be appreciated if noted. Remember that sherry is practically the only aperitif with a predictable and relatively constant alcohol titre: it's unfashionable but can be used to emphasise a slightly old world air of belonging to a Distinguished Profession. As for lunch itself, your position will be easiest if it is chosen for you. If you are given the menu, treat it casually and get someone else to lead. Suppress your ordinary reflexes ruthlessly: your instinctive look for the table d'hôte and hope that it'll be under 12*s.* 6*d.* is irrelevant, as this is of course on an expense account (or on several), and the more that is spent now the less is wasted in excess profits taxes. Also no individual dish will cost less than 15*s.*, and this sort of fact is normally unnerving. Hold it till the waiter makes suggestions, and be too bored to reject them. He has more experience than you of the kind of entry this particular business likes in its accounts. Drink will happen, and by this time you should have decided whether there still might be an honorarium for you in the offing, or not. Accordingly, you choose between discretion and exploitation, and if the latter, there are no special problems for some time. Even with discretion you will probably be unembarrassed about the choice of a cigar, but there is no point in being blasé. As for the actual object of the lunch, which was to discuss a job of some sort, that is perfectly simple. Listen receptively and appreciatively, and when just before you go the subject is raised again, ask for the matter to be put in writing, as you'd like a day or two to think what you can add to your already extensive commitments. This will take you back to square one and let you treat the whole thing seriously, and if the proposals never come, who are you to complain after a lunch like that?

* * *

A round of Christmas visits suggests that my medical friends share a predilection for the same form of heater for surgery premises. It rose phœnix-like from hearth after hearth, but to me the only warming thing about it was the splendid unashamed oxymoron of its name—an electric coal fire.

No doubt, some are excellent and really simulate a cheerful coal-fire, but most convey nothing more than a fire that is dying. My first instinct is to seize the poker, the rake, the bellows, have the chimney swept, or speedily arrange to convert to central heating.

Are only general practitioners addicted to it? Does it represent an atavistic link with witch-doctor forebears, summoning and quenching flames at will? But, what flames! The true promethean fire is a golden red and the flames are almost ivory. These false fires with their dull red and mauve bits of gauze and plastic have the colours of dying embers. Carefully powdered with realistic ash, the " glow " struggles through, and

the whole seems to need a good clean draught—if not a completely new fuel merchant. If there are logs they were obviously purchased from a rascally street-hawker, and the hearth was built by a pathetic and doomed do-it-yourself character from a Pinter play.

Of course the whole thing may be a subtle sabotaging of the Coal Board's propaganda plug. Certainly " there's nothing like *this* coal fire ". Not even a pyromaniac could find a good word for it.

* * *

I shall remember 1960 as an exceptionally good year for spiders. I am quite fond of the very small ones, and have no serious objection if, for instance, one suddenly appears swinging between me and my poised forkful of bacon-and-egg, or scuttles anxiously out of sight when I open *Lady Chatterley* or last week's *Lancet*. But I find it difficult to feel kindly or even tolerant towards the large, ugly sort, despite the belief that these are sensitive, intelligent creatures with a refined taste in music. And cobwebs, large or small, are on the whole rather unpleasant things once the sparkling dewdrops or other poetic additions have dried off. This year, not only the usual corners and crevices but indoor plants, pictures, and lampshades have grown an extra trimming of little grey frills overnight, and everywhere one has recoiled from unexpected, invisible barriers at face-level. Any disturbance of gardening tools, mouldy wellingtons, or other useful junk in shed and garage set off sinister arachnoid wrigglings in the dark depths; or sometimes an unlovely brute, surprised in his squalid festooned corner, crouched uncertainly, looking neither sensitive nor intelligent. Their proverbial diligence, too, has passed all bounds. Bruce's spider was a mere dilettante compared with the one which nightly spun a grisly polygonal curtain across the rear window of my car. I was quite surprised, indeed a little disappointed, one morning when there was no curtain to wipe off. I was just beginning to regret my ruthlessness when I noticed that the convenient space between two spokes of the steering wheel had been filled in.

It was while I was indignantly removing this insult that I had the uneasy thought that I might be losing opportunities, that fame might be passing me by while I went blindfolded by a duster. Should I by now have rediscovered the ancient virtue in cobwebs, and perhaps even devised a method for synthesising it? I can only hope that the new year will be as spiderous, and that readers will regard this as a preliminary communication.

* * *

Your readers will be familiar with the conditions of gastric stomach and cardiac heart, but I met a variation which was new to me in the orthopædic outpatients today when a mother asked me to examine her daughter's feet because she was afraid that they were developing joints.

* * *

News from the Nursery.—In the eighth month of my pregnancy one of my other little horrors handed me a screwed-up bit of paper. " Swallow this ", he said, " with an aspirin and you're not to read it." Deftly palming the missive, I unrolled it later out of sight. " You're not half going to cop it when you pop out," I read.

* * *

MY INSTITUTE

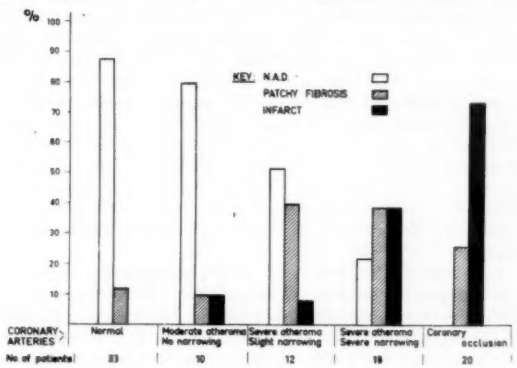
With bursting pride I saw my monster rise—
My Institute, whose girders scrape the skies.
The hammer and the shattering drill to me
Were like the quires of angels' minstrelsy.
Finished at last! The final painter's mate
Went down the lift and clanged its brassy gate.
In clouds of straw we now unpack the gear;
Machines with splendid knobs and dials appear,
Machines which type the answers and, it's said,
Will write your thesis while you snore in bed.
And now, white-coated, my assistants stand,
With fair technicians all at my command.
Already foreign visitors with smiles
Beg reprints from our vast enamelled files.
I stand there dumb. The visitors are waiting.
I can't remember what we are investigating!

Letters to the Editor

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Although some time has elapsed since the very important letter in which Dr. Robb-Smith [1] discussed this subject, I trust that in view of the importance of the problem you will allow us to comment.

As Dr. Robb-Smith points out, you, Sir, have clearly stated [2] that in the last analysis patients do not suffer from coronary disease but from the resultant ischæmia. While myocardial ischæmia may result from several causes,[3] by far the most important is disease of the coronary vessels.[4] Dr. Robb-Smith refers to the ischæmic myocardial lesions found in elderly persons and rightly points out that this sphere of cardiac pathology is still unexplored: in our opinion the true incidence



Cardiac blood-supply in relation to cardiac ischæmia.

of this myocardial scarring will remain unexplored until representative sections are examined from each heart at each necropsy: the present system of sectioning only those hearts which show frank naked-eye lesions of the muscle has led insensibly to what might almost be termed an " all-or-nothing " belief—i.e., that myocardial ischæmia presents only as a large lesion obvious naked-eye at necropsy. In point of fact, however, as regards numbers, these large frank lesions may be likened to that portion of an iceberg which rears above the surface while the great mass of the iceberg (the microscopic lesions) go undetected.

As Harrison and Wood [5] pointed out, this focal myocardial fibrosis is the result of minute infarcts, and it is our failure to recognise the high incidence of such minute infarcts that has so confused our thinking on the subject of myocardial ischæmia and myocardial failure. It is essential that we now recognise that in Western countries at least in individuals over middle age, the scarred heart like the mildly scarred kidney is the common finding not the exception: as is only to be expected, the degree of myocardial scarring bears a close relationship to the degree of narrowing of the coronary arteries, ranging from a mild isolated fibrosis where the narrowing is slight to gross myocardial infarction where the artery is severely affected. This straight-line relationship was well illustrated by our report [6] on Bantu hearts, and is equally clear in our unpublished work on Canadians and Australians (see accompanying figure of findings in a Canadian series).

Department of Public Health,
Public Health Laboratory Service,
Perth Chest Hospital,
Hollywood, Western Australia.

WM. LAURIE
J. D. WOODS.

1. Robb-Smith, A. H. T. *Lancet*, 1960, ii, 1029.
2. *ibid.* 1959, ii, 863.
3. Blumgart, H. L., Schlesinger, M. J., Davis, D. *Amer. Heart J.* 1940, **19**, 1.
4. *Wld Hlth Org. tech. Rep. Ser.* 1959, no. 168.
5. Harrison, C. V., Wood, P. *Brit. Heart J.* 1949, **2**, 205.
6. Laurie, W., Woods, J. D., Roach, G. *Amer. J. Cardiol.* 1960, **5**, 48.

PNEUMOCONIOSIS

SIR,—We believe that the letter from Dr. Oakley (Dec. 24) will be welcomed by many who have been confronted with this situation. It could, however, be pointed out that this problem is, if anything, more relevant to foundrymen than miners.

The foundry worker is less accustomed to the word pneumoconiosis and less accustomed to look on " dust in the lungs " as a more or less inevitable mark of the trade. More cases and more X-ray abnormalities are being reported because of the greater amount of chest X-ray investigation that has followed the increased awareness by both trades unions and employers of pneumoconiosis as a foundry problem.

We hesitate, however, to have the pneumoconiosis panels regarded as the arbiters of anything except entitlement to compensation, which is their function. We should in turn like to see that function performed in such a way that possible misapprehension is minimised.

We have often to take great pains to interpret the letter which states " . . . you are not *suffering* from pneumoconiosis ". The italics are ours, but we think that they should be used in the Board's letter, if indeed this phrase must be used. Experience shows the harm that can result from apparent conflict between doctors in these cases. We are failing in our duty as a profession if we do not make efforts to clear up areas of disagreement. Some of these arise from differences merely in definition and terminology, others from the confusion of radiological categories introduced for scientific convenience with disablement classification expressed as percentages for insurance purposes.

If experts in the treatment of pneumoconiosis think that such confusion is only in the minds of the patients and not of doctors, perhaps they can help with the following two queries. The answers might enable some of us to tackle the problem of the pneumoconiosis patient at work with increased confidence and a clear conscience.

(1) Are we justified in terms of truth as in terms of expediency in reporting or implying " Your chest is within normal limits " to a category-I pneumoconiosis?

(2) Do the pneumoconiosis panels ever report to the symptomless category-II patient " You are not suffering from pneumoconiosis " and if so, with what justification?

To tell a man that the panel are the judges of whether there is " enough dust in the lungs " to justify certification is useful in some cases, but so manifestly untrue that its use is questionable. On the other hand, one could tell a man that the panel are not there to question a diagnosis, but to judge from special tests how disabled he is, and from special knowledge how far this is due to his work. This again may not be strictly true, but does at least express a pious hope.

Our excuse for writing is to enter the plea that in the interests of the patient we should put our house in order in these matters. If further knowledge must be acquired or promulgated to this end no effort must be spared.

West Bromwich. C. W. D. COLE.

Birmid Industries Ltd., Smethwick. GILLIES MACBAIN.

PSEUDOACANTHOSIS NIGRICANS

SIR,—Patients presenting with pigmented lesions of the acanthosis nigricans type are always very worrying in view of the possible presence of some internal malignant process, and Dr. Tighe (Dec. 31) is to be congratulated on her recent paper drawing attention to the not uncommon " benign " variety or pseudoacanthosis nigricans.

I have recently had under my care an obese man aged 51 who started with pigmentation of the axillæ, groins, gluteal cleft, and sides of the abdomen some three months before I first saw him. Although he was thought to be in the " benign " group, he was investigated extensively for internal malignant disease with completely negative results. In addition to those given by Dr. Tighe, there are two further useful points of differentiation between the " benign " and " malignant " variety, both of which were demonstrated in my patient. The first is a positive family history, which is not uncommon in the " benign " variety; and the second is that in the " malignant " variety the palms and sometimes the soles show a peculiar hyperkeratosis which is very aptly described by MacKenna as " velvety ". In my experience this velvety hyperkeratosis of the palms is not seen in pseudoacanthosis nigricans.

Oxford. H. R. VICKERS.

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—It is to be regretted that Dr. Russell Barton (Dec. 17) has taken such a narrow approach in considering this important problem. Indeed, it could be said that Diogenes had wider horizons. To assert that many consultants, S.H.M.O.S, and medical advisory committees are incompetent and to conclude that medical-superintendent administration is the only efficient method is retrograde thinking.

Clark [1] has recently reviewed some of the principles he believes important in medical administration. The concept of an efficient and active medical superintendent and a vigorous medical staff advisory committee living symbiotically as part of the same administration is another method of producing the same end-result which he describes. In both methods new ideas are allowed to emerge from a broad front and in depth. Authority and spokesmanship remain democratically operative in a system where experience and knowledge are given full rein.

Opportunities are present for the grasping, and Dr. Russell Barton is doing himself a disservice in what he has said. The onset of new legislation is a time for taking stock and a golden opportunity for the use of new attitudes in mental-hospital practice. Most are agreed that there must be a readily available spokesman for the doctor. The medical superintendent is by experience and past practice the person ideally suited for such a post. Moreover, he already exists. The principles of democracy have shown that committees working in the correct field represent a sensible way of ensuring that justice is done. A medical staff advisory committee can fulfill these purposes provided that the following conditions are met:

(1) The medical superintendent is never chairman.
(2) The officers are elected democratically.
(3) The minutes of each meeting are submitted regularly to the hospital management committee.
(4) The committee must have direct access through its chairman to the hospital management committee.
(5) The chairman attends management committee meetings.

An efficient medical superintendent has nothing to fear from the medical staff advisory committee and much to gain: it gives support to him in his dealings with the hospital management committee and he has always a forum which he can consult. In this way the objections to Dr. Kidd's scheme are overcome and Dr. Duffield's views are fully met. It has been said that a medical staff advisory committee can exist only if allowed to do so by the medical superintendent. This is no longer of moment when the above conditions have been met.

With this scheme the stage is set for a medical administration that allows the best from everyone, if he is prepared to give it. If Dr. Russell Barton's views can be applied to the whole of the psychiatric profession, then as the years go by, so the medical staff advisory committee will become defunct and we shall have shown ourselves to be unable to devise a better scheme than has hitherto existed. I do not subscribe to this opinion at all, and as Dr. Bardon says (Dec. 17), the institution of the new Mental Treatment Act is an opportune time for new approaches to this challenging problem.

It is under these circumstances that the qualities of a medical superintendent are of supreme importance.

1. Clark, D. H. *Amer. J. Psychiat.* 1960, **117**, 506.

Professional men need leading, not driving, and the efficient medical superintendent will, above all else, do this very thing. Besides being alive to the progressive changes in mental hospital practice and its relationship to the community, he will also be able to live tolerantly with an active medical staff advisory committee, of which he will never be chairman. This takes courage, but in my view the progressive hospital of the future will show this healthy and virile relationship and is more likely to attract consultants and S.H.M.O.s who are prepared to think, knowing that although they have a spokesman they can also have their say. It is not inappropriate that a special allowance has been made to medical superintendents by the findings of the Royal Commission, for it is richly deserved. In short, the course of medical administration in mental hospitals must be steered between the Scylla of the autocratic medical superintendent and the Charybdis of a democratic medical staff advisory committee. It is not an easy pathway for the future, but we, at Hellingly, feel that we have taken some steps towards that better understanding.

Hellingly Hospital, Hailsham, Sussex. R. MAGGS.

SETTING A WHALE TO CATCH A SPRAT

SIR,—May we comment on a statement in your annotation of Dec. 3?

You say " cervical smears may reveal a few cases of cervical carcinoma but will miss an equal number or suggest the presence of carcinoma when it is not there ". Cervical smears seldom miss a carcinoma. If they do, it is usually a clinically obvious case with gross contamination by blood and necrotic material. So far as we know, no patient in our series has been harmed by delay in diagnosis due to this cause. Your " equal number " was reached by comparing 11 cases of clinically unsuspected invasive carcinoma detected by smears with the 9 false negatives for the whole series including advanced cases.

As for smears which suggest the presence of carcinoma when it is not there, we agree that invasive carcinoma is not the only cervical lesion which produces positive smears. The whole range of abnormalities which we have called epithelial instability, including " carcinoma-in-situ ", all produce abnormal smears, and without the cytological method it would be hard to find these cases at all. When no abnormality is found on biopsy, we believe this to be due to failure to select the right area for biopsy.

We agree about the whale, but some patients with " carcinoma-in-situ " develop invasive malignancy. Is it such a sprat?

M. M. BODDINGTON
R. H. COWDELL
A. I. SPRIGGS.
United Oxford Hospitals.

SUNBURN OF THE RETINA

SIR,—About a year ago we reported [1] a considerable number of cases of small paramacular solar burns in the eyes of people who had looked at the sun using inadequate filtering during the eclipse of Oct. 2, 1959. Most of them were children, and follow-up of some of them has demonstrated that many of these lesions have persisted with in most cases a small residual scotoma.

We note from our diaries that a further partial eclipse is due in this country on Ash Wednesday, Feb. 15, 1961, and we feel we should draw doctors' attention to the grave dangers of looking at the sun with the naked eye or inadequate dark glasses. Flynn pointed out [2] that the only safe way of watching the sun's face at any time is by projecting an image of the sun from a pinhole in a piece of card on to another piece of clear card, and that in no circumstances should those without special training and knowledge attempt to inspect the sun's disc directly.

M. J. GILKES
D. ST. CLAIR ROBERTS
A. H. OSMOND
B. THORNE THORNE.
Sussex Eye Hospital, Brighton.

1. *Brit. med. J.* 1959, ii, 1487.
2. Flynn, J. A. F. *Med. J. Aust.* 1960, i, 85.

THE ROCKING CHAIR

SIR,—Dr. Swan (Dec. 31) says he is " struck by the excellent mental and physical state " of those who use rocking chairs, and attributes their good health to the light and leisurely exercise of their forearm and calf muscles. I think he is right in his observation but wrong in his inference.

The wellbeing of his North American patients is, I think, due not to local muscular exercise resulting from very limited exertion, but to the universal cellular and visceral exercise which results from the rocking, and is therefore obtained without any exertion at all.

During the late war I invented a mechanical swing which has since been greatly improved, and now I sleep most nights in an electrically propelled model. Some kind of swing or hammock was used therapeutically by the ancient Greeks for " passive exercise ": they had a word for it—αιώρα. In fact, their physicians recommended four kinds of passive exercise—oscillatory movement in a hammock, sailing, horse-riding, and car-drives. I have given a detailed explanation [1] of what happens in the course of the first of such exercises.

Many disabled persons would particularly benefit from this internal exercise which entails no exertion, displacement, external movement, or manipulation. I believe that further scientific research in this hitherto unexplored field would yield rich rewards.

London, E.C.4. JOSEPH YAHUDA.

IRREDUCIBLE INTUSSUSCEPTION

SIR,—In the interesting 30-year survey of intussusception in childhood (Dec. 24) Mr. Campbell Cooke and Dr. Lewis express the opinion that " resection . . . is the method of choice " in irreducible cases.

In November, 1935,[2] you published a paper of mine advocating a short-circuit to relieve the intestinal obstruction, leaving the intussusception in situ.

I do not wish to become a voice crying in the wilderness, but I would urge that this method of treating these desperately ill babies be considered as an alternative to resection.

During the 25 years since 1935, improvements, chiefly in preoperative and postoperative treatment, have led in cases undergoing resection to a fall in mortality from nearly 100% to about 50%, but this high rate could be reduced further.

Since irreducible intussusception is comparatively infrequent, individual surgeons have little experience of treating these cases. I have treated only 6 since 1935, all except 1 by short-circuiting anastomosis. None has died: no peritonitis, and, apart from occasional attacks of colic during the first week and some fever for about two weeks, no adverse symptoms have developed from gangrenous bowel retained within the alimentary canal. The exception was a case in which my overzealous efforts at reduction split the ensheathing layer and made resection unavoidable. Fortunately, after an anxious few days, this child survived.

The surgeon faced with an irreducible intussusception should remember two facts: it is intestinal obstruction that kills these children—peritonitis occurs only rarely; and, secondly, young children withstand intestinal resection badly.

The contention that a short-circuiting anastomosis " offers little, if any, saving of time over resection " is not a valid

1. New Biology and Medicine. London, 1952.
2. Elliot-Smith, A. *Lancet*, 1935, ii, 992.

argument as time per se is relatively unimportant: it is the trauma inflicted which matters; and in this instance an ileo-colostomy is surely less traumatic than a resection. Likewise death following a "successful" but difficult reduction must be due in part to surgical trauma and this can be avoided by early cessation of attempts at reduction and treatment by short-circuit rather than by resection.

Possibly some children who survive this procedure may in later life develop features of the "blind-loop syndrome"; but to use an aphorism often quoted by the late Prof. Grey Turner, "Better a living problem than a dead certainty".

Oxford. A. ELLIOT-SMITH.

POSTOPERATIVE THROMBOEMBOLISM

SIR,—Your leading article [1] draws attention (by means of at least 2 incorrect references) to some interesting work on coagulability of the blood during and after operation. However no definite conclusions are reached and I think it appropriate to raise several practical problems.

Therapeutic anticoagulant treatment is of limited value but prophylactic treatment has had considerable success.[2 3] Certain types of operation—such as cardiovascular operations with their high rate of thromboembolic complications—justify anti-coagulant therapy over the operative period. Indeed any operation in which the surgery is "clean" and perfect hæmostasis is possible could be included. In the majority of operations, the possibility of bleeding during the immediate postoperative period presents greater problems than the very small number of thromboembolic episodes that occur.

To exhibit anticoagulants to a patient shortly before operation and hope to stabilise the level of prothrombin activity during the immediate postoperative period is, in my experience, extremely difficult and dangerous. I suggest that treatment instituted on the 3rd postoperative day will adequately cover the period when the majority of episodes occur and limit bleeding to a small group of patients.[3]

A special group of patients to be excluded are those already on long-term anticoagulant therapy for other reasons. In these patients the reaction to coumarin drugs is well known and considerable success is possible by merely reducing the level of prothrombin activity over the operative period.[4]

Finally, I am certain if clinicians realised the true incidence of embolic episodes contributing to death as revealed in careful postmortem studies that prophylactic postoperative anticoagulant therapy would become respected, even respectable.

John Bonnet Clinical Laboratories, Addenbrooke's Hospital, Cambridge. D. G. CHALMERS.

*** We apologise to Dr. Chalmers and others who were misled by our mistakes. Reference 1 in the leader should have been *Surg. Gynec. Obstet.* 1960, **111,** 469, and reference 5 *J. Amer. med. Ass.* 1959, **169,** 688.—ED. L.

PULMONARY HYPERTENSION

SIR,—As a former pupil of Dr. Pappworth's, may I comment on the recent controversy between Dr. Pappworth and Dr. Goodwin (Dec. 17), from the standpoint of the student rather than that of the experienced specialist?

The key to the matter seems to be the interpretation of *slight* right ventricular hypertrophy. To my mind the signs mentioned—left parasternal heave, loud P2, and narrow splitting of P2—are those of *well-marked* or *gross* right ventricular hypertrophy. Slight right ventricular hypertrophy is essentially an electrocardiographic diagnosis, completely lacking in detectable physical signs.

Narrow splitting of P2 as a sign of pulmonary hypertension is, I think, a sign which the average clinician who is not a full-time cardiologist would fight shy of. The diagnosis can be made by more easily elicited physical signs such as the parasternal heave, a loud P2, and a palpable impulse over the outflow tract of the pulmonary artery.

London, W.3. N. P. BURNS.

REDUCTION OF ANTERIOR DISLOCATION OF SHOULDER WITHOUT ANÆSTHESIA

SIR,—I read with interest Mr. Evans' paper of Dec. 31. He refers to Milch's method [1 2] as modified by Lacey and Crawford,[3] and he has obtained painless reduction in 43 out of 50 cases of anterior dislocation. In Edinburgh we have been familiar with this method following the comprehensive review by Mr. T. J. McNair.[4] McNair reported 90 successes in 100 anterior dislocations, with no complications, and his paper well repays study by those interested in this subject.

Edinburgh. JAMES A. ROSS.

SIR,—It can be assumed from Mr. Evans' clear account of the hanging-arm technique for reduction of anterior dislocation of the shoulder, that the method is becoming more widely known and used. Perhaps I might draw Mr. Evans' attention to the fact that the procedure was subject to a rigorous clinical analysis by McNair,[4] who used it in 100 consecutive cases. Mr. Evans' series supports McNair's conclusions that 90% of anterior dislocations can be reduced without anæsthesia by this technique and that it is free from complications.

Surgery Department, University of Aberdeen. HUGH DUDLEY.

DEATHS UNDER DENTAL ANÆSTHESIA

SIR,—A death was recently reported [5] under dental anæsthesia associated with trichlorethylene, the second in similar circumstances of which I have heard in the past two months.

In both cases hypoxia was undoubtedly present—the indicated O_2 was 5% during administration in the case of which I have knowledge—and the stage was well set for disaster by the added presence of trichlorethylene. Nothing abnormal was found post mortem in either case, and I suspect this is the usual story.

Trichlorethylene properly used is unquestionably safe as many can confirm from hospital experience, but the difference between hospital and dental cases is cardinal. In hospital oxygen is never wittingly restricted, and mixtures containing 20–25% O_2 or more are given from the outset. In dental outpatients, regularly subjected to oxygen concentrations as low as 5%, the practice of introducing trichlorethylene or any other volatile agent into a subatmospheric oxygen tension seems exceptionally dangerous, increasingly so with the severity of the hypoxia. I doubt whether trichlorethylene is any more dangerous than ethyl chloride, divinyl ether ('Vinesthene'), or even halothane ('Fluothane'), if similarly misused.

Kyle [5] hints at an unrecognised "faint" as a possible cause of the death he reports. Trichlorethylene is not an agent noted for its hypotensive effect; halothane is, yet no deaths from this agent in dental anæsthesia have been reported, so far as I am aware.

Fainting during dental anæsthesia seems to have been a widespread but unjustified fear of dental anæsthetists ever since

1. *Lancet*, 1960, ii, 1433.
2. Sevitt, S., Gallagher, N. G. *ibid.* 1959, ii, 981.
3. Chalmers, D. G., Marks, J., Lloyd, O., Bottomley, J. E. *ibid.* 1960, ii, 220.
4. Owren, P. A. Symposium on Anticoagulant Therapy (in the press).

1. Milch, H. *Surgery*, 1938, **3**, 732.
2. Milch, H. *J. Bone Jt Surg.* 1949, **31A**, 173.
3. Lacey, T., Crawford, H. B. *ibid.* 1952, **34A**, 108.
4. McNair, T. J. *J. R. Coll. Surg. Edin.* 1957, **3**, 47.
5. Kyle, D. W. *Brit. dent. J.* 1960, **109**, 332.

Bourne's work was published.[6] Yet this fear should long since have largely been allayed by Goldman et al.[7] whose findings were a sustained *rise* in blood-pressure in every one of 100 cases under N_2O. Indeed this is the normal response to hypoxia, no doubt accentuated by anxiety or fear. Fainting is not in my experience the response of the frightened, save in the reactionary period, whether one considers the dentist's chair or the emotional stresses of everyday life. Goldman et al. confirm this *reactionary* fall in all their cases. Fainting during anæsthesia must be a very rare hazard indeed.

Though I do not believe that halothane is the ideal for all general anæsthesia, I claim it is invaluable in dental outpatients and will come to be more widely used. Given with full oxygenation, as it must always be, it seems as suitable for the preschool child as the traditional "brewer's drayman", and could on present evidence supplant the generally satisfactory but far from ideal "straight N_2O". Meanwhile, if trichlorethylene must be used as an adjuvant in a difficult case, the O_2 percentage must be increased immediately to 20% within a few breaths, and N_2O regarded mainly as a vehicle.

Exeter. P. BUTLER.

A SIGN OF SURGICAL EMPHYSEMA

SIR,—Dr. Raison (Dec. 24) has modestly avoided a claim for originality in his observation of a curious nasal intonation in patients with surgical emphysema. Sampson,[8] in fact, has described a "nasal twang to the voice" in patients with spontaneous rupture of the œsophagus. With some diffidence I quoted Sampson's observation in a recent work of mine since, like Dr. Raison, I felt that the sign might be of negligible value. Now I believe it may have some clinical importance because a few weeks ago I had admitted under my care a patient with the signs and symptoms of a perforated peptic ulcer.

This patient had a most unusual nasal twang to his voice, and for this reason I had the chest radiographed as well as the abdomen. Air was seen in the neck, in the mediastinum, and under the diaphragm. A few hours later emphysema was detected clinically in the neck. Operation was impossible because a cardiac condition made the patient quite unfit for general anæsthesia. At necropsy there was found the unusual combination of a perforated duodenal ulcer and a supradiaphragmatic rupture of the lower end of the œsophagus.

Gayton, Cheshire. JOHN A. SHEPHERD.

TRANQUILLISERS IN PSYCHIATRY

SIR,—Your leading article of Oct. 15 on this subject was authoritative and accurate. I should, however, like to point out an important omission. There is a third class of drugs, besides the phenothiazines and the reserpine-like alkaloids, which should be classified among the neuroleptics. The prototype of these compounds, haloperidol, has been adequately described in at least 62 clinical and pharmacological papers, the first one being published in England.[9] Haloperidol is 4′-fluoro-4-{1-[4-hydroxy-4-(4′-chloro)-phenyl-piperidino]} butyrophenon.

This compound is effective in various schizophrenic conditions; it is liable to produce extrapyramidal symptoms and is similar, pharmacologically, to the more potent piperazinopropyl-phenothiazines. In animals, haloperidol is up to 200 times more active than chlorpromazine; it is better absorbed orally and has a longer duration of action. Clinically its usual maintenance dose is of the order of only about 3 mg. by mouth daily, and in this sense it is more potent than any of the available phenothiazines.

Haloperidol is now being used extensively on the Continent for the treatment of various schizophrenic conditions. The drug is also used as an anti-emetic and as a pre-anæsthetic agent. Haloperidol is undergoing extensive clinical trials in Britain and the United States. It was discussed on June 22, 1960, at the Royal Society of Medicine in London, when eight papers on the subject were presented by English investigators.

Research Laboratorium Dr. C. Janssen, Beerse, Belgium. PAUL A. J. JANSSEN.

PREMEDICATION WITH ATROPINE BY MOUTH

SIR,—We apologise to Dr. Gusterson for missing his paper The Management of Children Undergoing Tonsillectomy,[1] in which he refers to premedication with atropine by mouth.

We appreciate the point in Dr. Murphy's letter of Dec. 10, but should like to say that we planned our controlled study in order to eliminate, as far as we could, the coincidence that Dr. Murphy mentions, and we found that, whether the atropine was given by mouth or by injection, similar effects were produced.

The object of our trial was to determine whether absorption of atropine from the intestinal tract is unpredictable as Dr. Murphy says, and the results proved otherwise.

Dr. R. J. Hamer Hodges, of Portsmouth, has kindly written to us to say that he has not used atropine by injection for any child older than three years since 1955, and has drawn our attention to two further references.[2 3]

Guy's Hospital, London, S.E.1. M. C. JOSEPH
R. J. VALE.

PROTEIN IN HYALINE MEMBRANE

SIR,—The statement in your excellent leading article[4] that "no effective remedy is in sight" prompted me to send you the following preliminary data.

When studying the effect of administering pure O_2 on the respiration of premature infants, using a body-plethysmograph, I found that initially the volume of the lungs increased (raised functional residual air), and then the depth and frequency of respiration.

There were indications that the raised functional residual air when breathing O_2 is a consequence of hyperæmia of the lung vessels producing "lung-erection"; and that the increased depth and frequency of respiration are an adaptation to this.

Since in experimental animals exposure to O_2 can produce hyaline membranes in the lungs, I thought that the symptoms of the respiratory-distress syndrome in children might also be attributable to hyperæmia of the lung vessels, possibly brought about by changes in the circulation after birth. To reduce hyperæmia I have treated this syndrome by withdrawing 20–30 ml. of blood by catheter from the umbilical vein.

As Usher[5] has reported that in premature infants with this syndrome a toxic degree of reversible hyperkalæmia develops, I administered 10–15 ml. of 5% glucose intravenously after withdrawing blood to avoid this possibility.

I treated five babies with weights ranging from 1100 to 3100 g. All showed signs of the respiratory-distress syndrome and needed O_2. The serum-potassium of one infant was determined: it was 7 mEq. per litre. The serum of the others was hæmolytic. After treatment O_2 had to be given but they improved within 2 hours. After 12–24 hours supplementary O_2 was no longer necessary. All the children survived.

Snouck van Loosenziekenhuis, Enkhuizen, Netherlands. J. E. B. KALE.

6. Bourne, J. G. *Lancet*, 1957, ii, 499.
7. Goldman, V., Cornwell, W. B., Lethbridge, V. R. E. *ibid.* 1958, i, 1367.
8. Sampson, P. C. *Surg. Gynec. Obstet.* 1951, **93**, 221.
9. Janssen, P. A. J., van de Westeringh, C., Jageneau, A. H. M., Demoen, P. A. J., Hermans, B. K. F., Van Daele, G. H. P., Schellekens, K. H. L., Van der Eycken, C. A. M., Niemegeers, C. J. E. *J. med. pharm. Chem.* 1959, **1**, 281.

1. Gusterson, F. R. *Lancet*, 1955, i, 940.
2. Hamer Hodges, R. J. *ibid.* 1960, i, 82.
3. Hamer Hodges, R. J. Film presented at the Annual General Meeting of the Association of Anæsthetists, Great Britain and Ireland. Stratford, October, 1959.
4. *Lancet*, 1960, ii, 1014.
5. Usher, R. *Pediatrics*, 1959, **24**, 562.

A SINGLE-DOSE ANTHELMINTIC IN GENERAL PRACTICE

SIR,—In general practice the advantages are obvious of single-dose piperazine treatment for threadworms,[1] particularly where family therapy is necessary. The following short series of 21 cases—17 of threadworms and 4 of roundworms—illustrates the use of a granular preparation of piperazine phosphate and standardised senna (' Pripsen ').[2]

A single dose of the granules was given as advised by the manufacturers—i.e., gr. 160 (10·4 g.) to children of 6 years or over and adults, and gr. 120 (7·8 g.) to children under 6 years. The full dose contains 4 g. of piperazine phosphate and enough standardised senna to ensure that the paralysed worms are expelled before they can recover from the action of the piperazine. The dose was usually given at night, or for younger children in the morning, so avoiding the possibility of bowel action of the senna fraction occurring during the night. Where the infection was heavy, or where a number of children in a family were involved, a second dose of pripsen was given after two weeks, and in 2 resistant cases a third dose was also given.

The diagnosis in all the cases was based on symptoms, and in 13 it was confirmed by the presence of worms in the stools. Cases were considered cured when, following treatment, the symptoms had disappeared for six to eight weeks. Absence of symptoms for twelve weeks seems to indicate not only that the individual has been cured but also that the source of infection in the home has been eliminated.

The single-dose piperazine treatment was very successful (see table), and 3 cases of roundworms and 5 of

CHILDREN TREATED WITH PRIPSEN IN GENERAL PRACTICE

Case no.	Sex	Age (yr.)	Symptoms	No. of doses	Follow-up period (wk.)
Threadworms:					
1	M	5	Severe	3	12
2	F	4	Mild	2	7
3	F	6	"	2	7
4	M	7	"	2	7
5	F	8	Severe	2	7
6	F	7	"	2	5
7	M	5	"	2	12
8	M	7	"	2	12
9	F	3	Mild	1	12
10	M	8	Severe	1	8
11	M	4	"	1	10
12	F	2	Mild	3	6
13	M	2	Severe	2	12
14	M	3	"	2	12
15	F	5	Mild	2	12
16	F	8	"	2	12
17	M	3	"	2	12
Roundworms:					
18	F	6	"	2	12
19	F	12	Severe	2	8
20	F	8	Mild	2	8
21	M	10	"	1	6

threadworms which had resisted other forms of treatment responded readily. The only failure was a particularly difficult case, which did not respond even when treated in hospital.

When a threadworm infection has been established for four weeks or more, particularly in a family with a number of children who share the same bed, all the children, and probably the parents, are likely to be infected. Treating only patients with obvious symptoms will often fail, whereas treating all the children or the whole family usually eradicates the infection.

The single-dose treatment of the troublesome cases which so often resist repeated seven-day courses of piperazine was very successful. The two methods have produced equally high cure-rates in controlled trials.[2 3] This tends to confirm one's fears that family treatment so often failed in the past because the seven-day course was seldom completed by the symptom-free members. In 5 of my cases the infection was eradicated from the household by the administration of a single dose to each member of the family. But I think a second dose after two weeks is advisable.

The 4 cases of roundworm infection were readily cured with a single dose of piperazine, but a second dose was given in each case to ensure that the infection did not recur.

The neurotoxic and other side-effects which have been seen with seven-day courses of piperazine did not arise in any of my cases. Vomiting was troublesome in 1 child with roundworms (case 19), but it was present before treatment was attempted.

Leek, Staffs. G. KAGAN.

1. *Lancet*, 1960, i, 1177.
2. White, R. H. R., Scopes, J. W. *ibid.* p. 256.
3. White, R. H. R., Standen, O. D. *Brit. med. J.* 1953, ii, 755.

TREATMENT OF NASAL CARRIERS OF STAPHYLOCOCCI

SIR,—The report of the treatment of nasal carriers of pathogenic staphylococci by Dr. Stratford and his colleagues (Dec. 3) indicates that ' Soframycin ' nasal spray results in 100% clearance of the organism. The conclusions may result in the widespread use of this compound in the control of carriers and the treatment of sinusitis. For this reason, it should be emphasised that gramicidin, contained in the preparation soframycin, when sprayed in the nasal cavity will cause areas of micro-consolidation in the lungs.[1] This compound, therefore, should not be employed until further studies show that soframycin is non-toxic in this regard.

Cleveland Metropolitan General Hospital, Cleveland, Ohio. CHARLES H. RAMMELKAMP.

CONVENTIONAL VOLTAGE ELECTROPHORESIS FOR FORMIMINOGLUTAMIC-ACID DETERMINATION IN FOLIC-ACID DEFICIENCY

SIR,—The excretion of excess formiminoglutamic acid (FIGLU) in the urine after histidine loading has been shown to be a sensitive test for folic-acid deficiency.[2] Current methods of measuring FIGLU are either complex and laborious or involve expensive equipment. Knowles and his colleagues [3] recently reported a new method of detecting urinary FIGLU using high-voltage electrophoresis. Their observations suggested to us that it might be possible to detect FIGLU in specimens of urine subjected to conventional electrophoresis on cellulose-acetate strips. Such a method would have the advantage that it could be carried out in any routine laboratory.

The method is based on the electrophoretic separation, detection, and estimation of FIGLU in the urine of patients to whom 15 g. of *l*-histidine have been given. FIGLU is separated together with glutamic acid by cellulose-acetate electrophoresis using conventional apparatus and power supply with a pH 5·4 pyridine-acetate buffer and a current of 200 V at 0·5 mA per 1 cm. width on a 12–14 cm. long strip.

Peak excretion of FIGLU usually occurs between 3 and 8 hours after administration of the histidine and a sample collected at this time is used. Aliquots of the patient's urine are applied in duplicate on a strip together with a marker containing a measured amount of FIGLU added to a control urine. After a run of 25–30 minutes the strip is dried and cut into two parallel halves. One half is exposed to ammonia vapour, converting any

1. *J. infect. Dis.* 1942, **71**, 166.
2. Luhby, A. L., Cooperman, J. M., Teller, D. N. *Proc. Soc. exp. Biol., N.Y.* 1959, **101**, 350.
3. Knowles, J. P., Prankerd, T. A. J., Westall, R. G. *Lancet*, 1960, ii, 347.

FIGLU present to glutamic acid which will then stain with ninhydrin. Both strips are dipped in acid alcoholic ninyhdrin solution and placed in an oven at 80–90°C for 5–10 minutes in order to develop the colour. With this technique three spots can be seen on each strip; the spot nearest the cathode corresponds mainly to histidine, the one near the application line in the centre contains glycine, and the spot towards the anode is glutamic acid. If FIGLU is present in the urine it can be detected only on the ammonia-exposed strip as a spot corresponding to the mobility of the FIGLU marker and merging with the glutamic acid spot. A semi-quantitative estimation of the amount of FIGLU present can be obtained by comparing the intensity of the colour of the marker spot with the patient's FIGLU spot.

Our results of some 85 tests on 60 patients have shown this technique to be a simple, practical, and apparently sensitive method for the detection of folic-acid deficiency. In all 18 cases of folic-acid deficiency, including 7 patients with idiopathic steatorrhœa, increased urinary FIGLU has been present. Good correlation has also been found with the serum "folic-acid" level [4] and with the clinical response to therapy.

Queen Mary's Hospital, Roehampton.
J. KOHN.
Department of Hæmatology, Postgraduate Medical School, London, W.12.
D. L. MOLLIN
L. M. ROSENBACH.

VIRUS TUMOURS OF MICE

SIR,—Your interesting article [5] on virus tumours in mice refers to criticisms of Dr. Gross's work which claim that he has not demonstrated the viral origin of leukæmia.

On the other hand, it is asserted in connection with the Bittner virus that breast cancer in mice can undoubtedly arise in its absence. I do not know how, in the present state of our knowledge, one proves that a virus is not there; the fact that breast cancer follows exposure to cholanthrene, or leukæmia exposure to radiation, no more excludes a microbial origin in these conditions than the fact that pneumonia follows exposure to smog or tuberculosis follows exposure to industrial agents refutes the microbial origin of these diseases. All four events may be merely examples of the fact that, as Oberling [6] points out, disease seems to be highly conditioned by such factors as heredity, hormone imbalance, and trauma.

In cancer we are concerned not merely with tumour formation: we are concerned with disease. It is curious therefore that so little discussion centres round what is, after all, the $64,000 question. Is malignant disease a single disease of specific origin in the sense that tuberculosis, actinomycosis, or pernicious anæmia are single diseases? It is often asserted that we can and do know the answer to this key question; in fact, we can only judge the probabilities.

If malignant disease is a single disease it obviously cannot be both viral and non-viral in origin. If it is not a single disease, and there seems little doubt that at present this particular interpretation of the facts is most widely accepted, the question arises: why have the different type of malignant disease so many clinical and pathological features in common? Doubtless the answer will be: "Because of the presence of tissue-infiltrating tumours." This proposition is, however, purely an assumption on our part; it has never been demonstrated that the insidious, progressive asthenia, to the clinician one of the hallmarks of the disease, is the result of the abnormal cellular growth.

However admirably the somatic mutation theory may explain the carcinogenesis of malignant disease, it throws no particular light on the equally important asthenia of malignant disease.

The hypothesis suggested by the discoveries of Peyton Rous, Bittner, and Ludwig Gross, that malignant disease is a viral toxæmia, normally but not inevitably accompanied by the formation of tissue-infiltrating granulomata, has a great deal to commend it on clinical grounds.

Weybridge, Surrey. A. FOXE.

TREATMENT OF FANCONI'S ANÆMIA

SIR,—Dr. McDonald (Nov. 19) describes treatment of two siblings with Fanconi's hypoplastic anæmia with a combination of prednisone and testosterone, following a report [1] of successful treatment of aplastic anæmia in children with these drugs. McDonald and Goldschmidt,[2] describing five cases of Fanconi's anæmia (including the two siblings), reported failure of corticosteroids to affect the anæmia, an experience which seems to be common to all reported studies. The following details of successful use of prednisolone in Fanconi's anæmia may be of interest.

A $2^1/_2$-year-old boy was admitted in November, 1956, in congestive cardiac failure after a respiratory infection; the hæmoglobin was 2·9 g. per 100 ml., leucocytes 6800 (neutrophils 30%), and platelets 9600 per c.mm.; there was moderate macrocytosis. After intramuscular digoxin a transfusion of packed cells raised the hæmoglobin to 7·9 g. and the platelets to 32,000, but bleeding from lips and rectum occurred some days later. Marrow biopsy showed hypoplasia of all cell systems. He was much underweight at 19 lb., his mentality was slightly retarded, and there was congenital dislocation of both hips. The mother had died 2 years previously (cause uncertain); one brother had died in this hospital 2 years before from "aplastic anæmia"; a sister had died at home some years before after respiratory symptoms (she was said to be pale); a male infant had died some hours after birth; and three sisters were said to be well. A 15-year-old brother was seen on two occasions, and the peripheral-blood picture suggested mild hypoplastic anæmia; he has only 3 digits on each hand; the bone-marrow was not studied.

20 days after admission a further transfusion of packed cells raised the hæmoglobin to 11·8 g. Five further transfusions of packed cells were necessary in the next 8 months, hæmoglobin falling to 2·9–5·9 g. between transfusions. After the seventh transfusion in November, 1957, prednisolone 40 mg. daily was started, the dose being reduced gradually to 10 mg., to 7·5 mg. 5 months later, and to 5 mg. daily after some further months, on which dose he has since remained, apart from substitution of 4 mg. triamcinolone daily for a period of some months. No further transfusions have been needed; in May, 1960, hæmoglobin was 92%, leucocytes numbered 4100 with normal differential count, and platelets appeared normal on films. Trial stoppage of steroids for a month on one occasion led to a recurrence of anæmia which responded to resumption of these drugs. He has since been admitted to a long-stay orthopædic hospital, where a recent blood-count was normal. Despite continued attempts to increase food intake, appetite and growth remained poor, weight being only 24 lb. at age 6 years; protein-anabolising hormone was without effect.

With regard to the incidence of hypoplastic anæmia associated with congenital abnormality, it is likely that two or three of this patient's siblings have the same hereditary disease. I have also had under my care a grossly obese hydrocephalic boy with severe pancytopenia which did not respond to steroids and in whom repeated transfusions were necessary until he died after 18 months. An elder sister has a peripheral-blood picture consistent with hypoplastic anæmia; there is a congenital

4. Baker, H., Herbert, V., Frank, O., Pasher, I. Hutner, S. H., Wasserman, L. R., Sobotka, H. *Clin. Chem.* 1959, **5**, 275.
5. *Lancet*, 1960, ii, 200.
6. Oberling, C. Riddle of Cancer; p. 152. New Haven, 1944.

1. Shahadi, N. T., Diamond, L. K. *Amer. J. Dis. Child.* 1959, **98**, 293.
2. McDonald, R., Goldschmidt, B. L. *Arch. Dis. Childh.* 1960, **35**, 367.

abnormality of one thumb, but she has not yet returned for marrow examination. It is likely that the anæmias of these last two patients also belong to the Fanconi group.

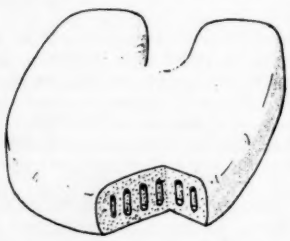
Even though successful treatment with steroids is gratifying, the long-term prognosis must surely be guarded. The cause of the basic defect being at present unknown, it is interesting to speculate on the mechanism of action of steroids in those cases in which they act beneficially; do they compensate for some specific hormonal lack, or is there a genetically determined auto-immune mechanism?

I wish to thank Prof. J. D. Kennedy and Prof. M. E. Folan for the laboratory work, and Dr. O. C. Ward for a recent report on the patient.

Regional Hospital, Galway. BRIAN MCNICHOLL.

A RECESSED CUSHION

SIR,—A recessed cushion makes life easier for invalids who are chair-ridden, and promotes healing in those who have pressure ulceration. It is more stable and less demoralising than the old-fashioned air-ring and may be covered with waterproof material if necessary.



When it is used in a modern chair on tubular springing there is the added advantage that free ventilation is provided and the cushion may be transferred to the wheelchair or motorcar when occasion demands.

The cushion illustrated was made for me by Parker Knoll of High Wycombe.

High Wycombe. DAVID ELLIS.

TROPICAL EOSINOPHILIA

SIR,—Please permit me to say that Professor Webb and his colleagues, in their excellent and interesting paper,[1] have, perhaps through an oversight, left out the evidence I presented in 1949 of the association of filariasis with tropical eosinophilia.[2]

In 6 out of the 7 cases I reported, clinical and laboratory evidence of filariasis was present, and in the 7th case the cause appeared to be *Tænia solium* infestation. The cases with actively motile microfilariæ in the peripheral blood were also reported in *The Lancet*.[3] In all these 4 cases, in addition to microfilariæ in the peripheral blood, the lungs were affected and the blood showed leucocytosis and eosinophilia. 3 had asthmatic attacks, and, in 3, eosinophils were found in the sputum.

In fact, I advocated the use of diethylcarbamazine as early as 1949 [2]; and later events showed that diethylcarbamazine was to have an important place in the treatment of eosinophilia.[4]

Professor Webb and his coworkers point out that earlier evidence,[5 6] as well as their own well-documented observations, confirm the filarial hypothesis of the ætiology of tropical eosinophilia. The pathological evidence they put forward is of the greatest importance, for it confirms the longstanding observation that filariasis is a cause of this condition. There is nothing wrong with this view provided we accept that there are other causes too. Diethylcarbamazine produces an excellent response in eosinophilia, but it is too early to come to Sir Philip Manson-Bahr's conclusion that this provides almost conclusive evidence that the eosinophilic response is parasitic and not allergic.[6]

I have found diethylcarbamazine effective also in allergic coughs *not* associated with eosinophilia, and in hayfever, in postinfluenzal coughs, and in some allergic dermatoses. I have also seen eosinophilia develop in some patients after influenza.[7] The puzzle of tropical eosinophilia, therefore, remains a puzzle and after a full circle we are comfortably back to Löffler's original view that the disease is allergic. Perhaps we know a lot more now about the agents that cause this allergy, such as filariasis, tæniasis, ascariasis, and other helminthic infestations, mites, and viruses,[8] &c., especially the influenza viruses. The therapeutic action of diethylcarbamazine also remains a puzzle, like that of its illustrious predecessor, arsenic, for it apparently has much larger frontiers than a humble antifilarial agent.

Gauhati, Assam, India. S. L. MALHOTRA.

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2. Malhotra, S. L. *Ind. med. Gaz.* 1949, **84**, 292.
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AGRANULOCYTOSIS ASSOCIATED WITH PARACETAMOL

SIR,—Agranulocytic angina has not hitherto been attributed to paracetamol (N-acetyl-*p*-aminophenol). Ten years ago a compound containing this substance, together with aspirin and caffeine, was withdrawn from the market by E. R. Squibb because three cases of agranulocytosis or severe leucopenia had occurred while patients were taking it, but the relation between the syndrome and the drug was never established.

When paracetamol was introduced it was subject to medical prescription for three years before being released by the American Food and Drugs Administration for sale to the general public. During the past ten years the substance has been freely available in many countries and no case of agranulocytosis attributable to its use has yet been reported. The following case may therefore be of some interest:

A woman of 78 had enjoyed good health for many years. In November, 1959, she was troubled with increasing stiffness in the legs, due to early osteoarthritis, and began to take paracetamol ('Panadol') for relief. She took 2–3 tablets a day for many weeks, then increased the dose to 4 tablets daily.

On June 20, 1960, feverish symptoms developed and rapidly increased. On June 22 the temperature was 104°F and next day she became delirious. That day she was put on dimethyl chlortetracycline ('Ledermycin') and she had received 600 mg. or possibly 900 mg. before I saw her next day.

At this time fever was still high and she was intermittently confused in mind. There were sordes at the angles of the mouth which had developed in the past twenty-four hours. The tongue was dry and red and the soft palate and fauces showed extensive, superficial, greyish-yellow ulceration. The left tonsillar gland was enlarged but not tender. Crepitant rales were heard over the lung bases but there was no clinical evidence of pneumonia, nor of any severe infection, and a radiograph of the chest next day was normal. The liver edge was palpable, but the spleen was not enlarged.

Blood-count on June 24 showed hæmoglobin 13·3 g. per 100 ml., white cells 600 per c.mm. (neutrophils 40%).

She was admitted to hospital and given penicillin G 1 million units twice daily. All other drugs were stopped. Her recovery was steady, as serial counts show.

June 24	white cells	600, neutrophils	240 per c.mm.
June 25	" "	900, "	360 " "
June 27	" "	1000, "	510 " "
June 29	" "	2250, "	1210 " "
July 2	" "	4500, "	3040 " "

The cause was not at once apparent. There was clearly no overwhelming infection and the picture was just such as is typical of drug-induced agranulocytosis. Her doctor was not

aware of her penchant for paracetamol, but when she had recovered sufficiently she made it clear that apart from occasional doses of senna and paraffin, neither of which had been needed recently, the only drug she had been taking was paracetamol. It is certain that she took this every day up to the onset of the fever and possibly also on the first and second day of the illness. She had never been given dimethyl chlortetracycline before so that allergy to this drug could be ruled out, and anyway the symptoms began three days before the antibiotic was started.

Test doses of the suspect drug will sometimes cause a recurrence of fever with leucopenia when the patient has fully recovered, but while a positive reaction of this kind is diagnostic a negative one means nothing. I did not think that such a test was justifiable in this case and am forced to conclude that paracetamol was almost certainly the provocative agent.

City General Hospital, Gloucester. T. W. LLOYD.

THE FAMILY DOCTOR

SIR,—The article by Dr. Balint and your leading article of Jan. 7 raise issues of fundamental importance for the future of the family doctor.

Judging by the spate of recent publications on this subject, it seems that, in Mr. Foster Dulles's words, an "agonising reappraisal" of the family doctor's role is in progress. Very few, if any, of these articles have seriously questioned the value of either a personal or a family doctor in an age of increasing specialisation, so it seems that the profession has already answered "Yes" to Professor Rutstein's question "Do you really want a family doctor?" It is, however, doubtful whether many of the family doctor's supporters realise how uncertain is his survival with the profession organised as it is at the moment.

The National Health Service has put down an iron curtain between general practice and the hospitals. Interchange between the two has become virtually impossible; the family doctor is excluded from hospital, except as a player of minor roles; and the number of hospital doctors with experience of general practice is dwindling rapidly. No wonder that highly trained and qualified men do not want to go into general practice. And yet, if the family doctor—as the only man retaining the whole view of the patient—is to interpret and evaluate the reports of specialists, surely he should be as highly trained and as good, academically, as the specialists themselves. To carry out Professor Rutstein's proposal for a separate curriculum for family doctors, or to accept Dr. Balint's distinction between scientific medicine and "whole person" medicine, would be to complete the fragmentation of our already divided profession. Far from family doctors evaluating and coordinating the results of specialists, they would no longer even speak the same language.

Unless this iron curtain is lifted I do not think that general practice can survive in any worthwhile form. Severed from the fountainhead of scientific medicine in the hospitals, the family doctor's faculties may well atrophy until he becomes little more than a psychotherapist. Conversely the hospital doctor will lose the perspective and sense of proportion which come from experience in general practice. It should be entirely natural for a man to do five years as a hospital registrar, then go into general practice. It should be equally natural for him to move after five or ten years in general practice to the post of full-time consultant, where he will advise other family doctors, or to a teaching post, where he will train future family doctors and specialists. A man of ability with such a training and experience would be well equipped indeed as a consultant or a teacher. But no such man would be drawn to general practice as it is at the moment.

Why should not general practice and the hospitals be integrated, so that men with the required credentials can be physicians or surgeons in hospital as well as being family doctors? The tendency towards group practice should make it easy to absorb such men into general practice. Since they would perform much of the routine medicine and surgery, they would solve the chronic problem of finding intermediate staff for non-teaching hospitals. General practice would gain immeasurably from an infusion of new blood; the hospitals would benefit from closer contact with family doctors; the profession as a whole would be integrated rather than fragmented and, most important of all, the patient would find, both inside and outside hospital, doctors who can take the holistic view of medicine advocated by Dr. Balint.

Stratford-upon-Avon. IAN R. MCWHINNEY.

THE GENERAL PRACTITIONER AND THE HOSPITAL

SIR,—In this town, the local hospital—a small general hospital—has 6 clinical assistants who are general practitioners. Thus, every firm of doctors has a member attached to the hospital. This privilege was not secured without a struggle.

Speaking for myself, I can say that I look upon the contact with a hospital as a great benefit and privilege. My impression is that, after some early misgivings, the consultant staff are well satisfied with our work. X-ray and pathological facilities are of course available to us.

Bridlington. P. D. H. CHAPMAN.

PSYCHIATRIC ASPECTS OF ACUTE PORPHYRIA

SIR,—Acute porphyria is rare in this country, and the diagnosis is not always borne in mind [1]: one reason is that the predominating features are often neuropsychiatric, and thus the weight of responsibility for recognising the condition lies heavily on the psychiatrist.

Of the 8 patients described by Whittacker and Whitehead,[2] 3 had been in mental hospitals and 3 others had psychiatric symptoms at some stage during attacks. 3 of the 5 cases described by Markovitz [3] had been referred in the first instance to a psychiatrist. Hirson [4] described mental symptoms in 2 cases, a hysterical picture and a confusional state; and the 2 cases described by Hare [5] were similar. These in fact represent the characteristic psychiatric syndromes, as Hare noted—either a confusional state or a rather nebulous picture with depressive and hysterical features.

The number of recorded case-histories seems sufficiently small to justify reporting the following two cases.

CASE 1.—A married woman of 23 was admitted to a general hospital in December, 1957, with pyelitis in the third month of pregnancy. Within a few days, after treatment with sulphonamides, she became anxious and depressed and was seen by a psychiatrist who advised methyl phenidate ('Ritalin'), promazine ('Sparine'), and barbiturate at night. Her depression continued, however, and she was very apathetic, with some retardation. Accordingly, she was transferred to a mental hospital where it was proposed that she should have a course of electroconvulsive therapy. Sulphonamides were continued, with oral iron and vitamins, and she still had a barbiturate at night. Two days after admission retention of urine and abdominal pain developed, and, on catheterisation, the urine was dark but not the typical port-wine colour of porphyrinuria. Treatment was not suspended until two days later, when porphyria was first suspected, and subsequently confirmed. By this time she had been on sulphonamides and barbiturates for over a week.

During the next four days her general condition improved, the urine became lighter, control of micturition returned, and there were no neurological signs; but she remained in a state of slightly retarded depression, and she still had abdominal

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2. Whittacker, S. R. F., Whitehead, T. P. *Lancet*, 1956, i, 547.
3. Markovitz, M. *Ann. intern. Med.* 1954, **41**, 1170.
4. Hirson, C. *Brit. med. J.* 1953, i, 1372.
5. Hare, E. H. *J. ment. Sci.* 1953, **99**, 144.

pain. Next day she had a bilateral lower motor-neurone paresis of the upper limbs and some slurring dysarthria. This peripheral neuropathy rapidly progressed to complete flaccid quadriplegia and she died.

CASE 2.—An unmarried woman of 21 was admitted to the neurological wing of a mental hospital in December, 1959. The urine was normal. She had been seen at home the day before admission. She was lying in bed, and immediately spoke: " I start to shake and I grind my teeth; I have no control of anything; everything becomes stiff." She then turned on her left side with her face drawn to the left in tonic spasm, or alternatively arched her back in a state of opisthotonus, staring at the ceiling. There was some myoclonic twitching round the mouth, but nothing else to suggest that the attack was other than hysterical. The girl's mother was in distracted attendance, and it was clear that their relationship was much less mature than the daughter's age.

The patient was a life-long enuretic, and some six months before coming under our care, she had had a course of propantheline bromide (' Pro-Banthine '), with some temporary improvement in the enuresis, but this recurred after a few weeks. Three months later she had a febrile illness with some signs of meningeal irritation, for which she was admitted to an isolation hospital, but this quickly resolved, and at no time were there any abnormal findings in the cerebrospinal fluid. Since the illness she has had a few attacks of apparently hysterical type, culminating in the one which brought her under our care. Apart from the enuresis, there had been no previous abnormality.

An E.E.G. showed dysrhythmia of non-specific type. The resting record showed unstable occipital alpha, and slow waves persistent in the posterior regions of both hemispheres. Runs of mixed sharp waves and theta activity seemed localised to the left side. Overbreathing augmented, and photic stimulation blocked, all activity. Although there was no focal area, there appeared to be sufficient in the record to suggest a trial of anticonvulsants, and she started phenobarbitone and phenytoin sodium (' Epanutin '). Five days later she had developed abdominal pain with pyrexia (100°F) and some tenderness over the bladder. A catheter specimen of urine was taken, and in view of the tenderness and subsequent instrumentation, she was given a course of sulphonamides, but this was stopped when there proved to be no growth on culture of the urine. For some days thereafter she lay in bed, apparently distressed by the continuous pain, but having none of the attacks which she had had before admission. Later she also complained of some aching pains in the legs. The urine appeared normal, but a test [6] for porphyrinuria was positive. Phenobarbitone was immediately withdrawn, and during the next two weeks, she gradually improved; the phenytoin was continued and her further progress was uneventful.

Hare [5] presumed that the mental symptoms in acute porphyria were due to actual brain damage, but considering the fluctuations of the clinical course, Hierons'[7] view seems more acceptable—that there is a direct metabolic effect comparable to the pharmacological action of mescaline, and the effect may be reversible.

The importance of this condition to the psychiatrist is twofold: the possibility of porphyria should be borne in mind whenever a toxic-confusional state is associated with severe pain, dark urine, or limb weakness and wasting; and the importance of the effect of barbiturates and sulphonamides in precipitating acute attacks in patients with latent porphyria, especially since barbiturates are so commonly given in mental illnesses. Gillhespy [8] described deterioration in a patient who had had E.C.T., and it seems generally agreed that E.C.T. is contraindicated in porphyria.

In case 1, pregnancy may have been a further precipitating factor. Vine et al.[9] concluded that pregnancy tended to exacerbate porphyria, but Freedman et al.[10] described a woman who improved during and after pregnancy, and Waldenström [11] questioned whether the pregnancy itself was responsible rather than drugs given during this period.

How many of the generally accepted contributory factors are the effects of treatment rather than a cause of porphyria? In case 2, for example, it seems quite possible that the ill-defined, possibly encephalitic, illness which preceded the hysterical episodes, was an attack of porphyria, perhaps precipitated by the course of propantheline. Roth [12] remarks, and Hare [5] reiterates, that acute porphyria tends to occur in persons of neurotic constitution: this is doubtless so, but the history of many patients with porphyria is so often a lamentable tale of long and inconclusive investigation, misdiagnosis, and ineffective or harmful treatment, that it seems reasonable to assume that some of the " neurotic constitution " is acquired rather than constitutional.

As Saint et al.[13] suggested, the Watson and Schwartz test [6] should be used more often in the diagnosis of obscure abdominal and peripheral pain, unexplained hysterical, depressive, and confusional states, and neuropathies.

I wish to thank Dr. G. E. Duggan-Keen and Dr. S. Smith for permission to publish details of the two cases, and Dr. Smith for his helpful suggestions.

Lancaster Moor Hospital, Lancaster. M. D. CASHMAN.

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7. Hierons, R. *Brain*, 1957, **80**, 191.
8. Gillhespy, R. O. *Lancet*, 1954, **i**, 908.

RETICULOCYTOSIS INDUCED BY β-METHYL ASPARTATE

SIR,—We have postulated a relationship of threo-β-methyl aspartate to thymine biosynthesis via carbamyl methyl aspartate [14] and have demonstrated a sparing of vitamin B_{12} by methyl aspartate in the growth of ochromonas.[15]

We have obtained data on a patient with pernicious anæmia who was treated orally for $5^1/_2$ days with 800 mg. β-methyl aspartic acid followed by $7^1/_2$ days' treatment with ureido-β-methyl succinate followed by 10 days' treatment with β-methyl aspartate.

A reticulocyte response was noted on the 8th day which reached a maximum of 8% on the 10th day of treatment. No rise in hæmoglobin or red cells was noted during a 23-day period of observation. Subsequent intramuscular vitamin B_{12} administration was followed by a rapid onset of a reticulocytosis of 18% on the 3rd day of vitamin-B_{12} therapy. An uneventful remission was then obtained.

A sense of wellbeing with increased strength and appetite was noted during each course of β-methyl aspartate. This subjective response was absent while the ureidosuccinate was being given.

It seems that the reticulocyte response, the subjective and appetite response, and the speed of response to B_{12} are indicative of a vitamin-B_{12}-sparing action by β-methyl aspartate, but not by the ureido-β-methyl succinate.

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ELI SEIFTER
ARTHUR SAWITSKY
JAMES I. BERKMAN
HENRY D. ISENBERG.
Long Island Jewish Hospital, New York.

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AMINE-OXIDASE INHIBITORS AS POSSIBLE TREATMENT FOR PHENYLKETONURIA

SIR,—Pare et al.[1–3] suggested that the mental defect in phenylketonuria may be partly caused by decreased concentrations of 5-hydroxytryptamine (5-H.T.) and perhaps other monoamines in the brain. If so, then any method of increasing its concentration in the brain might prove rational therapy. Some years ago we tried to do this by treating affected children with iproniazid, which inhibits monoamine oxidase, the enzyme responsible for much of the further metabolism of biologically active monoamines.[4] This treatment would thus tend to raise the concentrations of 5-H.T. and of catecholamines in the tissues.

Eight phenylketonuric children aged 7–15 years were matched in pairs for sex, age, weight, and I.Q., and divided into two groups. One group was given iproniazid by mouth (50 mg. per day for 6 months); the other, an equal amount of placebo. Those responsible for evaluation of treatment were unaware which patients received the active drug.

TABLE I—SERUM-5-HYDROXYTRYPTAMINE (mg. per ml.) BEFORE AND DURING TREATMENT WITH IPRONIAZID (4 CASES) OR PLACEBO (4 CASES)

—	Before iproniazid	4 wk.	10 wk.	14 wk.	25 wk.	29 wk.
Iproniazid	75 108	96	78	88	220	132
	30 28	135	65	120	40	150
	64 57	180	108	115	84	160
	32 60	120	78	81	80	153
Placebo	.. ..	42	54	33	28	75
	54 75	96	120	91	70	88
	.. 60	42	36	36	72	72
	72 150	160	112	99	35	144
Sum of iproniazid	227	531	329	404	424	595
Sum of placebo	272	340	322	259	205	379
Iproniazid as % of placebo	84%	156%	102%	156%	207%	157%

Samples of blood and early-morning urine were collected before and at intervals after treatment began for estimation of 5-H.T. and urinary 5-hydroxyindoleacetic acid (5-H.I.A.A.) (see Pare et al.[1]). Regular estimations of glutamic-oxaloacetic transaminase were carried out.

There was no evidence during the trial that iproniazid benefited these children, as judged by behaviour, electroencephalogram, or intelligence testing. No adverse effects of the drug were noted.

Changes in the serum 5-H.T. and urinary 5-H.I.A.A. are shown in tables I and II. Although the results vary considerably, there is an overall increase in serum 5-H.T. during treatment with iproniazid, and a less definite fall in urinary 5-H.I.A.A.

Although only indirect evidence, these findings suggest that iproniazid may be raising the brain concentration of 5-H.T., as it does, together with catecholamines, in the experimental animal.[5] The fact that iproniazid did not benefit these phenylketonuric children is, perhaps, not surprising in view of their ages. Woolf et al.[6] state that treatment is unlikely to benefit children over 2 years of age, and then only if their I.Q. is more than 40. Irreversible brain damage does occur and it is likely that this begins early in life.[7] Now that safer monoamine-oxidase inhibitors are available, we feel that a trial of such a drug would be worth undertaking in young infants in whom irreversible brain damage is unlikely. This could ethically be undertaken when, for some reason, a phenylalanine-restricted diet is impracticable.

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5. Spector, S., Prockop, D., Shore, P. A., Brodie, B. B. *Science*, 1958, **127**, 704.
6. Woolf, L. I., Griffiths, R., Moncrieff, A., Coates, S., Dillistone, F. *Arch. Dis. Childh.* 1958, **33**, 31.
7. Crome, L., Pare, C. M. B. *J. ment. Sci.* 1960, **106**, 444.

TABLE II—URINARY 5-HYDROXYINDOLEACETIC ACID (mg. per g. CREATININE) BEFORE AND DURING TREATMENT WITH EITHER IPRONIAZID (4 CASES) OR PLACEBO (4 CASES)

—	Before iproniazid	2 wk.	8 wk.	10 wk.	16 wk.	27 wk.
Iproniazid	2·8 1·0	2·7	..	..	1·9	2·6
	5·4 3·5	3·6	3·0	2·9	3·3	2·5
	5·5 6·4	3·0	6·7	5·2	1·7	3·0
	2·3 5·8	4·6	1·8	2·5	1·8	2·2
Placebo	.. 2·0	1·7	6·7	2·8	3·0	3·6
	4·2 3·2	2·0	4·7	2·5	2·8	3·8
	2·5 2·6	1·7	4·0	..	2·5	2·9
	2·4 1·1	1·1	2·5	1·3	1·7	2·3
Sum of iproniazid	16·3	13·9	..	..	8·7	10·3
Sum of placebo	10·0	6·5	17·9	..	10·0	12·6
Iproniazid as % of placebo	163%	214%	..	..	87%	82%

We acknowledge the help of Prof. R. S. Stacey for estimations of serum-5-H.T. and of Dr. M. Sandler for those of the urinary 5-H.I.A.A. and serum-transaminase.

Fountain Hospital, London, S.W.17. BRIAN H. KIRMAN.

St. Bartholomew's Hospital, London, E.C.1. C. M. B. PARE.

ESSENTIAL-FATTY-ACID CONTENT OF HENS' EGGS

SIR,—Changes in hens' diets are known to affect the composition of the egg lipids.[1 2] Dr. Hugh Sinclair implied, during a recent television interview, that methods of poultry husbandry may also have a bearing on the dietary value of eggs. He preferred eggs from free-range or farmyard hens to those from battery hens in a human diet which he believed would lower the incidence of atherosclerosis in middle-aged men. This implies that free-range eggs contain more of the essential fatty acids (E.F.A.) which Sinclair has claimed are of value in preventing atherosclerosis.[3]

We are at present using gas-liquid chromatography to analyse the lipids of eggs from hens of similar breed housed under different conditions and receiving diets appropriate to the environment. We are determining the E.F.A. in the egg lipids and recording their values during the entire laying life of the birds.

A brief assessment of our results to date may be of interest because we have included both battery and free-range eggs in the study.

On average over two months, the lipids from free-range eggs contain 16·1% of E.F.A. and those from battery eggs 15·3%. This difference is unlikely to be of human dietary significance because the variation within each group was of the order ±1·2%.

There are indications that seasonal variations in E.F.A. contents are much greater than the differences between the two groups at any one time. Eggs produced under these two methods of husbandry are found to have closely similar E.F.A. contents, provided that they are sampled at the same time during the laying period.

Other workers have found a relationship between the E.F.A. content of eggs and of the diet of the hen.[1] In our experiment the diet of the free-range birds contained 1·52% of E.F.A. and that of the battery birds 1·24%. From our results so far there is an implication that the E.F.A. are slightly more effectively transferred to the egg in the case of the battery birds. We require more data before examining this point statistically.

In another experiment we supplemented the diet of battery hens with 4% arachis oil. The feed contained 2·5% E.F.A.

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Eggs from these birds had an average E.F.A. content of 18·8% over a period of five months.

At this stage in our work there is no evidence to support the claim that eggs from free-range birds are likely to have any real advantage over battery eggs as a source of essential fatty acids in the human diet.

The essential-fatty-acid content of eggs can be augmented somewhat, as indicated above, by increasing the E.F.A. content of the hen's diet, but whether this is necessary can be determined only in the context of human requirements, which seem difficult to evaluate in view of the complexity of existing dietary patterns.

Spillers Ltd., Technological Research Station, Cambridge. J. B. M. COPPOCK, N. W. R. DANIELS.

B.O.C.M. Ltd., Stoke Mandeville. W. P. BLOUNT.

The University, Reading. SYD FOX.

Public Health

Diphtheria in Camberwell

THE outbreaks of diphtheria in London and other parts of the country are disturbing. Between 1943 and 1957 the number of notifications in England and Wales fell each year, but in 1958 there was a sharp increase and there were 8 diphtheria deaths.

Camberwell, in south-east London, was free from diphtheria from 1948 to 1959, but from November of that year until early in February, 1960, 6 cases were reported, all in non-immunised children, and 70 others were found to be harbouring the organism. The outbreak was confined to one corner of the borough and was linked with a primary school.

There were no further cases until Dec. 19, 1960, when a child aged 7 years, living in another part of the borough $1^1/_2$ miles away, and attending a different primary school, was notified. The child had been ill for five days and went to school on the second day of her illness before being sent to a children's hospital. The school closed for the Christmas holidays on Dec. 21. Since then 29 children, most of them aged 6–7 years, who were either pupils at the same school or family contacts, have been sent to hospital—10 as clinical cases, the remainder for isolation and investigation following routine swabbing of class and home contacts. So far, no cases or carriers have come to light in people living outside the area near the school.

The present outbreak and the earlier one do not seem to be connected. *Corynebacterium diphtheriæ mitis* was the causative organism in both, but the recent cases tend to be more severe, many of them having the classical signs and symptoms, fortunately seldom seen today. A child of 7, a class contact of the first patient, has died.

While many of the carriers had received primary immunisation, in only 1 of the clinical cases was there any record of this, but a reinforcing injection had not been given. It is estimated that over 70% of children in this part of London have been immunised in infancy, but the proportion protected by a "boosting dose" at school age must be very much less. It is significant that nearly all the children affected in both outbreaks were of primary-school age.

Investigation and swabbing of the class contacts was complicated by the school holiday, but it was nevertheless accomplished quickly. As a result, active and passive immunisation was begun early. Some hundreds of children were brought to the special immunisation clinics opened on the school premises, and attendances at other clinics in the borough have shown a gratifying increase. The publicity given in the local and national press and on radio and television has, no doubt, also stimulated the public to cooperate.

Outbreaks such as this are a powerful reminder that failure to maintain a high rate of immunisation and reimmunisation may have disastrous consequences.

Respiratory Infections

Deaths attributed to influenza in England and Wales in the week ending Dec. 31, 1960, numbered 45; this was almost double the figure for the previous week (23) and for the corresponding week in 1959 (24). 40 of these deaths were of patients over 35, and 19 of patients over 74. Only 1 influenza death was reported from the administrative county of London.

Deaths from pneumonia in the same week totalled 910, as against 792 the previous week, and 748 in the corresponding week in 1959.

In the Midlands, many cases of respiratory-tract infection have been admitted to hospital, mostly with complications such as pneumonia, hæmorrhagic pneumonia, and cardiac involvement. Birmingham, Walsall, and parts of Worcestershire have been the worst affected within an area originally bounded by Stoke and Stafford in the north, Wolverhampton in the west, Hereford and Worcester in the south, and Birmingham and Walsall in the east. The epidemic is now spreading to the eastern Midlands, and Derby, Nottingham, and Burton-on-Trent are affected. Claims for sickness benefit in Birmingham are three and a half times, and in Burton two and a half times, the normal level. The Birmingham bed bureau's daily case-load of hospital admissions has been double that in the corresponding period in 1959.

Clear definition of the infection has been difficult because of the many cases of respiratory disease at this time of year. But many patients had the clinical signs and symptoms of influenza; and in 19 of them in Birmingham serological evidence of influenza-A infection was obtained. From 10 nurses and patients (some of whom were included among the 19 above) a virus of variety A2 was isolated. Influenza virus A was also isolated from a fatal case.

Medical and nursing staffs have been depleted; in 4 hospitals in Staffordshire, for example, 10% of the 400 nurses have influenza and this number is increasing at the rate of 10 to 15 a day. Many hospitals have been forced to restrict surgery to urgent cases.

We are indebted to Dr. C. W. Gordon, senior administrative medical officer, Birmingham Regional Hospital Board, for help in compiling this note.

Divided Responsibilities

In his report for 1959 Dr. R. J. Dodds, medical officer of health for Smethwick, comments on a growing tendency to pass on responsibility within the National Health Service. This, he says, can be traced back to a feeling in the earlier years of the N.H.S. that services were overlapping and being duplicated: in the field of home care instances were cited of 15–20 different visitors calling on the same family. The natural outcome was a proliferation of liaison and coordination committees, which in turn gave rise to numerous standing and ad-hoc sub-committees. All of these have done excellent work, but at a considerable cost in time, energy, and patience of highly skilled staff.

The next phase began when someone realised that only by contracting out of traditional obligations could the waiting-lists and vast building programmes be tailored to the limited national resources. Only patients needing active nursing and medical care were to be looked after in hospitals; other agencies would care for the remainder. Dr. Dodds states that the efficiency of a geriatric service appears to be gauged by only one index: the number of discharges per bed-year—and the more the merrier. Local welfare authorities, to whose care these patients are discharged, are not in general well equipped to deal with large numbers; and the problem is aggravated by the long-overdue abandonment of workhouse accommodation in favour of small homes which may lack facilities and staff to deal with the really infirm.

If the trend continues, more and more patients entitled to treatment and care may be unable to receive it because they do not fit into the restricted spheres of operation of hospitals and other institutions. Dr. Dodds suggests that as regards mental health in particular, with the new Act in force this tendency to pass on responsibility must be firmly resisted.

Infectious Diseases in England and Wales

Disease	Week ended December				
	3	10	17	24	31*
Diphtheria	3	3	2	2	18
Dysentery	646	563	533	544	271
Encephalitis:					
Infective	1	6	6	1	6
Postinfectious	3	2	4	4	2
Food-poisoning	144	165	164	89	98
Measles, excluding rubella	7248	7266	8559	8620	11,256
Meningococcal infection	16	17	19	19	17
Ophthalmia neonatorum	34	12	13	13	19
Paratyphoid fever	7	5	..	1	1
Pneumonia, primary or influenzal	273	297	294	357	481
Poliomyelitis:					
Paralytic	12	5	4	4	1
Non-paralytic	1	3	..	1	6
Puerperal pyrexia	173	147	147	122	131
Scarlet fever	536	530	497	447	383
Smallpox	..	..	..	..	..
Tuberculosis:					
Respiratory	381	415	344	314	271
Meninges and C.N.S.	3	2	10	3	..
Other	47	54	68	50	32
Typhoid fever	..	1	..	1	3
Whooping-cough	1096	1002	1024	734	678

* Not including late returns.

Appointments

BOWERBANK, SHEILA M., M.B. Durh.: school M.O., Co. Durham.
DAVIS, P. A. H., M.B. Dubl., M.R.C.P.I., D.C.H.: assistant M.O., Ramsgate area.
FORDYCE, F. W., M.B. Durh.: school M.O., Northumberland.
GILLATT, MAIRIDH A. M. N., M.B. Glasg., D.OBST., D.P.H.: senior M.O., central department, Staffordshire County Council.
LECKIE, F. H., M.C., PH.D., M.R.C.O.G.: consultant obstetrician and gynæcologist, Stobhill General Hospital, Glasgow.
PEARSON, VERONICA, M.B. Cantab., D.OBST., D.C.H.: assistant M.O., Halifax.
SPENCER, ELIZABETH M., M.B. Manc.: assistant M.O. and school M.O., Cumberland.
VACCARO, J. G., M.B. Lond.: assistant M.O.H. and school M.O., Chester.
WHITEHEAD, T. P., F.R.I.C.: biochemist (top grade), Queen Elizabeth Hospital, Birmingham.

Birmingham Regional Hospital Board:

ALLAN, W. S. A., M.B. Edin., M.R.C.P.E.: consultant pathologist, Wolverhampton hospital group.
KANJILAL, G. C., M.B. Patna, D.P.M., D.P.H.: consultant psychiatrist and deputy medical superintendent, North Staffs mental hospital group.
KER, W. A., M.R.C.S., D.P.M.: consultant psychiatrist, Mid-Staffs mental hospital group, with duties in the Wolverhampton group.
ROGERS, W. F., M.D. Dubl.: consultant physician, Stoke-on-Trent hospital group.

East Anglian Regional Hospital Board:

ALLANBY, K. D., M.D. Lond., M.R.C.P.: consultant physician, Peterborough and Stamford hospital group.
BUDHRAJA, S. N., M.S. Lucknow: surgical registrar, North Cambridgeshire Hospital, Wisbech.
CUTHILL, JUDITH J., M.B. Dubl.: registrar in psychiatry, Suffolk mental hospitals.
DIMOPOULAS, G. E., M.B. W'srand: surgical registrar (casualty), Peterborough Memorial Hospital.
GEORGE, A. D., M.B. Madras, F.R.C.S., F.R.F.P.S.: surgical registrar, West Norfolk and King's Lynn General Hospital.
GOLD, R. G., M.B. Adelaide, M.R.A.C.P.: senior registrar in cardiology, regional cardiological centre, Papworth Hospital.
KHAN, A. R., M.B. Karachi, D.T.M. & H.: registrar in geriatric medicine, south-west area.
SURYANARAYANA, B. V., M.B., F.R.F.P.S., D.T.M. & H.: medical registrar, Peterborough hospital group.

The Hospital for Sick Children, Great Ormond Street, London:

RAMSAY, ANDREW, M.B. Edin.: house-surgeon.
WASTELL, CHRISTOPHER, M.B. Lond., F.R.C.S.: house-surgeon.

Moorfields Eye Hospital, London:

GREAVES, D. P., M.B. Sheff., F.R.C.S., D.O.M.S.: part-time consultant ophthalmologist.
SMITH, R. J. H., M.S. Lond., F.R.C.S., D.O.: part-time consultant ophthalmologist.
TREVOR-ROPER, P. D., M.D. Cantab., F.R.C.S., D.O.M.S.: part-time ophthalmologist.

Medicine and the Law

Safe Working in Hospitals

EVERY employer of labour owes a duty to all his employees to provide what the law calls a safe system of working. The legal cases mostly concern workers in factories and mines, dockers, window-cleaners, and the like, but there is no reason to suppose that the principle does not apply to professional and technical staff as well. There are, of course, limits to this legal duty. The employer cannot guard against every possible danger. Provided he takes reasonable precautions (of which the practice of other employers may be evidence) and gives proper instructions to his staff, he will have discharged the legal responsibility laid upon him. Moreover, a great deal of work which has to be done is dangerous, and if it is not really practicable for the employer to diminish or eliminate the danger, then the risk of it is a necessary incident of the employment which the employee must accept.

These matters were touched on by Lord Thomson in a Scottish case concerning a male nurse who had contracted tuberculosis.[1]

The nurse, Joseph Sorman, sued the board of management of the Royal Scottish National Institution for Mental Defectives for £10,000, claiming that he had contracted tuberculosis while nursing mental defectives suffering from a variety of diseases including tuberculosis. The trial judge awarded £5000 damages to Sorman, but this award has been set aside on appeal.

Giving judgment on the appeal, Lord Thomson said that from the welter of confused thinking and conflicting ideas in which the evidence was entangled he was unable to unravel any consistent mode of dealing with the problem of nurses' health. The evidence had no practical relationship to what hospitals did or what they could do without going to limits of paternalism which they were, in effect, forbidden to attain. When one turned to the evidence of those who had practical experience of running hospitals one found that there was nobody who would say there was in actual practice any generally recognised system in operation. Everything was in a state of flux, and everybody was feeling their way.

Lord Thomson added that the degree of contact between Sorman and possible active tuberculosis was not such as to suggest that he was likely to run any appreciable risk.

1. *Glasgow Herald*, Dec. 3, 1960.

Obituary

W. E. M. WARDILL

W. H. H. writes:

"Wardill came back from retirement in 1952 to be professor of surgery in Baghdad. He remained for six years, which he always said were very happy ones. He never ceased to be amazed at the variety of clinical conditions which, in spite of his vast experience, he encountered for the first time in Baghdad, and he revelled in his collection of rare and beautifully mounted specimens. Severe burns from kerosene were all too common: Wardill found that the dry climate was ideal for the exposure method of treatment which he adopted with great success, and he made films illustrating the progress of his patients. Of a fatherly nature and fond of young people, he was in his element on teaching rounds with his students, who were all devoted to him, and he built up a team of conscientious young assistants whom he turned into first-class teachers: they are carrying on in his tradition."

Notes and News

WOMAN, WIFE, AND WORKER

WHY do married women go out to work? How do they manage their dual job? What problems do they create for their employers? What is the effect on their husbands and children? The admirable booklet [1] just published by the Department of Scientific and Industrial Research as the 10th of their series on *Problems of Progress in Industry* tries to answer some of these important questions. It is a summary of a detailed study of the industrial and domestic implications of married women's employment, and though it concerns workers in the factory of Messrs. Peek Frean & Co., Ltd., in Bermondsey, it will interest married women who do other kinds of work, whether skilled or unskilled, and also those who employ them.

Fifty years ago social reformers looked forward to a time when no married woman need leave her family to go out to work. But though it is already true that few *need* to work to provide bread for the family, many continue to do so for other reasons—their own growing need for interests and activities outside the home and the nation's continuing need for their services.

Most of the women studied went to work to earn money for their families, butter if not bread, but a strong subsidiary reason was the restricted and lonely life they led with small families in small houses, from which the husband and children were absent most of the day. "Coming to work keeps me young," some said. But they went to work to help the family, not escape from it. They regarded work as desirable, but not essential, and as less important than their family responsibilities. They were more concerned with fitting in their hours of work with family life than with prospects of promotion.

Little evidence was found to support the common belief that part-timers can only be regarded as temporary workers. If their needs were studied and their conditions of work adjusted accordingly, the part-timers were satisfactory workers, and in fact women without children tended to leave the factory more than those with children. Although absenteeism was greater among married women than among other workers, their absence-rate could be more or less predicted, thus minimising the disturbance it caused. A critical stage was reached when a certain proportion of part-timers in any one department was exceeded, and this saturation point should limit the ratio of part-time to full-time workers.

Also if work is to be done satisfactorily by part-time women, clearly those who supervise them must do a tremendous amount of planning and contriving, and show great understanding of the special problems of married women.

NOISE IN HOSPITALS

To be disturbing to people who are ill noise need not be loud. Sounds that would not look impressive on a noise-meter can cause distress and loss of sleep.

Two years ago King Edward's Hospital Fund for London published the results of an inquiry into noise control in hospitals.[2] In a follow-up inquiry in 1960 four additional hospitals (making nineteen in all) took part, and the results have now been published.[3]

The earlier finding that about half the patients were not unduly bothered by noise was confirmed, though there is a possibility that some grateful patients refrained from saying what they really felt. Clearly, some people are much more sensitive to noise than others; and some of the seemingly trivial noises complained of were a source of real irritation to a minority only. But, as the report says, if noise can be eliminated or reduced without detriment to treatment, it seems only right that this should be done.

There has been some improvement since 1957 in that fewer patients complained of noise from hospital fittings and equipment. More patients, however, remarked on traffic noise, and noise from other patients, crockery, and electric cleaning machines. Road traffic accounted for 29% of the complaints, and trolleys for 25%; "other patients" came third in the list with 17% of the total.

A surprising source of annoyance was the chiming of Big Ben, which was remarked upon in 21% of the questionaries returned from one hospital. 14% of the patients commenting from the same hospital complained of the noise of river traffic.

Some patients cheerfully accept a certain amount of noise, and a few remarked that they found it reassuring. As might be expected, it was excessive or unnecessary noise that gave rise to most complaints.

Traffic noise is the biggest problem, and one that is difficult or impossible to solve. Local authorities and police forces can sometimes help by diverting or controlling traffic. Structural alterations to hospital buildings, though effective, are often prohibitively costly. As the report suggests, hospital planners should bear in mind the necessity for the careful siting of new buildings and of extensions to old ones. The same consideration applies to rail traffic, and to noise from aircraft.

Complaints about noise from hospital equipment are still numerous, and many of the hospitals taking part in the inquiry stressed the importance of regular maintenance. One hospital gave an oil-can to each ward sister, apparently with good results from what has been termed "preventive maintenance".

Crockery and kitchen noises caused more complaints than in 1957—possibly because of the increasing use of stainless-steel sinks and draining-boards. Many of the hospitals are now making more use of equipment made of plastics, one of the most promising of which seems to be polypropylene.

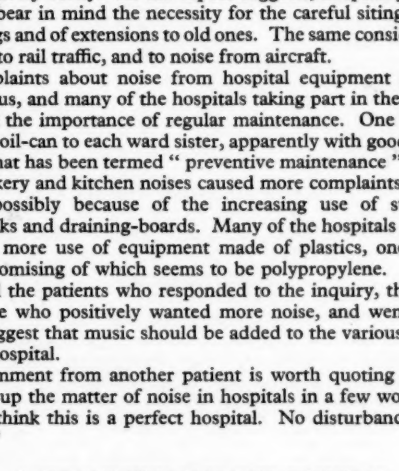
Of all the patients who responded to the inquiry, there was only one who positively wanted more noise, and went so far as to suggest that music should be added to the various sounds of the hospital.

A comment from another patient is worth quoting because it sums up the matter of noise in hospitals in a few words: "I should think this is a perfect hospital. No disturbance whatsoever."

A COT LOCKER FOR THE NEWBORN

Dr. Bernard Laurance writes from Derby:

"Any method that can reduce the number of times a baby is handled by a nurse, even for the changing of napkins, will help to lessen the risk of cross-infection in a maternity hospital.



This locker accommodates all that the mother needs for her baby.

"As shown, the locker attaches to any standard cot and is light enough to prevent the cot from up-ending. A bowl of

1. H.M. Stationery Office. 1960. 2s. (postage 2s. 4d.).
2. Noise Control in Hospitals, 1958. King Edward's Hospital Fund for London, 1958.
3. Noise Control in Hospitals. Report of a follow-up enquiry. King Edward's Hospital Fund, 34, King Street, London, W.C.2. 1960. Pp. 31. 1s.

water for swabbing the baby's buttocks can be placed on the 'Formica' top. Inside there is space for six to eight napkins which are replenished once daily, a swabbing bowl, soap, antiseptic buttock powder, and a jar of sterile cotton-wool.

"Once the mother is up, she fetches tap water in the bowl from the ward washbasin and a bucket for the soiled napkins, and changes the baby in the cot at her bedside. The young mother thereby learns to care for her own baby, and the overburdened midwife does not run the risk of infecting babies by handling them.

"These lockers have been used successfully in the Derby maternity hospitals for the past two years. They are made by Allen White & Sons, 176, Siddals Road, Derby, and the price is about £6."

AN EXPERIMENT IN NURSE TRAINING

In September, 1956, an experimental nursing course began at Glasgow Royal Infirmary. Its chief object was to prepare the student for the final State examination in two years instead of three, and enable her to act as a staff nurse during her third year. The experiment is expected to continue till 1961, but the assessment committee, of which Prof. J. H. F. Brotherston is chairman, have presented a report on the experience gained in the first three years. The report has been prepared by Miss M. Scott Wright, Boots fellow in nursing research in the University of Edinburgh.

The experimental course was more concentrated than the conventional course. Students received more formal instruction, and received it earlier in their course. Some subjects, including obstetrics, clinical psychiatry, and applied anatomy and physiology, were added to the curriculum. The amount of time spent on practical work was cut by more than half. For the whole of their first year and much of their second the experimental students were not regarded as part of the ward's nursing strength; no ward emergency was allowed to interfere with their training. Thus instead of being based on the traditional apprenticeship method, with alternating periods of classroom study and ward experience, the experiment was based on a deliberate balance and integration of theory and practice. This system needs a high ratio of teachers to students: the staffing ratio on the experimental course was 1 teacher to 10 students, compared with 1 to 42 on the regular course.

The assessment committee compared the performance of the students in the experimental course with the performance of two control groups (one in Glasgow and one in Edinburgh) who had received an orthodox training. The experimental students, who were on the whole better educated than the controls, did better in the theoretical part of the examination than either of the control groups. In the practical part of the examination the results were inconclusive, but in a ward practical test at Glasgow the experimental students, though they had had less practice, were equal—but not superior—to the control students.

On the other hand, by the end of the two-year course the experimental student was not ready to assume responsibility as staff nurse. At the beginning of the year she fell behind her control colleague in ward administration, team supervision, and—to a lesser extent—in nursing technique. By the end of the year the gap had lessened but still had not closed. But the transition from the protected atmosphere of the nursing school to full charge of a busy ward is bound to be harassing, and as the senior nursing staff gain more experience in coping with the situation the adjustment will probably be quicker and smoother.

It was also hoped that the new course would reduce wastage among the students and in this it seems to have had considerable success, for none of the first two groups of experimental students left before taking the final examination, whereas 15–20% of the controls did so. It must be remembered, however, that most of the students who failed to complete the course were those with an inadequate educational background, and none of the experimental students was handicapped in this way. They were also, no doubt, challenged by the novelty of their training, and this stimulus would flag if the new form of training became general. But even so the committee would expect the present high rate of wastage to fall.

Some of the experiment's most important aims were difficult to assess. It was hoped "to produce a more fully educated and mature nurse with scope for greater personality development". The benefits of the new methods of teaching will not, the committee feel, be evident for some time, but they feel certain that "a fuller educational process was established". About the development of maturity they were less certain, for they found some evidence of professional immaturity among the experimental nurses in their work as staff nurses.

According to the finance division of the Department of Health for Scotland, over the three-year period the experimental method costs about £250 per student per year more than the ordinary method; but this apparent extravagance might well prove an economy if wastage was avoided. More exacting are the course's requirements in the way of intelligence and education. The experimental groups were the pick of the Glasgow recruits and apparently left the ordinary course at such a disadvantage that they could not act as effective controls. The ratio of teachers needed is also high. Unless the new method be reserved for an élite, it would be interesting, before reaching a final assessment, to follow the progress of a group of average students trained in this way.

University of Birmingham

Last term the university received over £125,000 for research, including the renewal of a grant of 25,000 dollars from the Population Council, Inc., to the department of anatomy for ovarian studies, and a grant of £36,000 for a five-year period from the Nuffield Foundation to the department of medical biochemistry and pharmacology for work on the biological effects of oxidised fats.

University of Edinburgh

Lewis Cameron postgraduate prize (£45).—Applications are invited from graduates of not more than five years' standing for this prize, to be awarded for a paper on work relating to the diagnosis of disease. Papers must be submitted to the dean of the faculty of medicine by April 5.

Royal College of Physicians of London

Dr. H. G. Miller will deliver the Milroy lectures on Feb. 7 and 9 at 5 P.M., at the college, Pall Mall East, S.W.1. His subject will be Accident Neurosis.

The Congo

The International Committee of the Red Cross and the League of Red Cross Societies have launched an urgent appeal to national societies to send or to maintain medical teams in the Congo for a further period (*Times*, Jan. 10).

British Association of Allergists

The annual general meeting of this Association will be held on Saturday, Jan. 28, at 11 A.M., at 1, Wimpole Street, London, W.1. In the afternoon there will be a symposium on farmer's lung. Further particulars may be had from the secretary of the Association, Dr. A. W. Frankland, Wright-Fleming Institute, St. Mary's Hospital, London, W.2.

Nuffield Travelling Fellowships for General Practitioners

The Nuffield Foundation announces that the following fellowships have been awarded for 1961:

From the United Kingdom:

Dr. M. B. Lennard (Bristol) to enable him to visit Canada and the United States to study social and environmental factors in both undergraduate and postgraduate training in medicine.

Dr. R. A. B. Rorie (Dundee) to enable him to visit Canada and the United States to study general practice, with special reference to the incidence and treatment of the psychoneurotic and early psychotic case, for comparison with incidence and treatment under the National Health Service.

Dr. P. A. T. Wood (Ipswich) to enable him to visit the United States to study techniques and treatment of the respiratory viruses in general practice.

From Australia:

Dr. J. C. Yeatman (Unley Park, South Australia) to enable him to spend six months visiting medical centres in Canada, the U.S.A., and Great Britain.

Radioactive Substances Advisory Committee

Prof. B. W. Windeyer has been appointed chairman of this committee in succession to Sir Charles Darwin, who has resigned.

Royal Medico-Psychological Association

This Association is to hold a lecture course on Feb. 13 and 14 at 1, Wimpole Street, London, W.1. The speakers will be Dr. D. H. Bennett, Dr. D. H. Clark, Dr. A. B. Monro, Dr. Donald Blair, Dr. A. R. Sandison, Dr. John Randell, Dr. Alexander Walk, and Dr. W. Linford Rees. Applications for tickets should be sent to the secretary of the Association, 11, Chandos Street, W.1.

European Association against Poliomyelitis

This Association is to hold a symposium from Sept. 17 to 20 in Oxford. Those wishing to attend should apply to Dr. P. Recht, secrétaire général, 56, Rue Charles Legrelle, Brussels 4, Belgium, and those wishing to read papers should communicate with the secretary of the United Kingdom Committee for Poliomyelitis, Royal College of Physicians of London, Pall Mall East, S.W.1.

Mass Media and the Medical Officer of Health

The Central Council for Health Education is to hold a seminar on this subject from Feb. 21 to 24 at the Cora Hotel, London, W.C.1, when the speakers will be Dr. I. A. G. MacQueen, Dr. G. W. H. Townsend, Dr. H. D. Chalke, Mr. James McCloy, Dr. Richard Fox, Dr. I. A. MacDougall, Dr. C. S. Nicol, and Dr. Harvey Flack. Further particulars may be had from the medical director of the Council, Tavistock House, Tavistock Square, London, W.C.1.

Medical Inspectorate of Factories

Dr. T. A. Lloyd Davies is to succeed Dr. Sibyl Horner as Senior Medical Inspector of Factories.

Dr. Lloyd Davies qualified from St. Thomas's Hospital in 1932, and while holding resident appointments there he took the M.R.C.P. and the M.D. Later he was drawn to industrial medicine and became medical officer, and eventually chief medical officer, of Boots Pure Drug Company. In 1952 he was elected F.R.C.P., and shortly afterwards he took up his present appointment as professor of social medicine and public health in the University of Malaya. His book on the *Practice of Industrial Medicine* was first published in 1948. His other writings include papers on fitting industry to human needs, manganese peritonitis, the absence of Raynaud's phenomenon in workers using vibratory tools in a warm climate, and the medicosocial needs of old people in Singapore.

On Dec. 11 the Austrian Minister of Education presented Prof. Stefan Jellinek with the Cross of Honour for Science and Art (first-class).

A meeting of the Biochemical Society will be held on Saturday, Jan. 28, at 10.25 A.M., at Queen Elizabeth College, Campden Hill Road, London, W.8.

A committee meeting of the Group for Representation of the Views of Clinical Psychiatrists will be held on Thursday, Jan. 26, at 5.30 P.M., at Tavistock House North, Tavistock Square, London, W.C.1.

The Oxford Graduates' Medical Club dinner will be held on Friday, Jan. 20, at the Royal College of Physicians of London, Pall Mall East, S.W.1, when Dr. L. N. Jackson will be in the chair. Application for tickets should be made, before Jan. 16, to the secretary of the club, Miss Josephine Barnes, 7, Wimpole Street, W.1.

Ageing: its changes and its promise—Copies of the report of the conference, held last year at Blackpool, may be had from the National Old People's Welfare Council, 26, Bedford Square, London, W.C.1 (pp. 152. 5*s*.).

Hospital Abstracts.—The Ministry of Health is now publishing a monthly survey of publications on " matters relating to hospitals and hospital services (excluding strictly medical and related professional matters) " based on the periodicals, books, reports, and other material in the Ministry library. Each issue will contain about 150 summaries or notices in English, and the first appeared on Jan. 2. The journal is available from H.M. Stationery Office (annual subscription £3 4*s*.; 5*s*. per number).

Applications for an Eli Lilly medical research fellowship ($300 a month for twelve months and travelling expenses) are invited from doctors registered in South Africa who wish to undertake research in the United States. Further details can be obtained from Dr. H. A. Shapiro, P.O. Box 1010, Johannesburg. The closing date for applications is May 1.

A bursary has been awarded under the Royal Society and Nuffield Foundation Commonwealth bursaries scheme to Dr. W. H. Elliott, fellow in the biochemistry department of the John Curtin School of Medical Research, Australian National University, Canberra. He is to visit Cambridge to study microbiological techniques.

Diary of the Week

JAN. 15 TO 21

Monday, 16th

UNIVERSITY COLLEGE LONDON, Gower Street, W.C.1
5.30 P.M. Prof. F. Bergel: Biochemistry and Biology of Enzymes in Cancer.
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Prof. Sheila Sherlock: Cirrhosis of Liver.

Tuesday, 17th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. D. A. Pond: Psychiatric Aspects of Epileptic Brain Damaged Children. (First of two Goulstonian lectures.)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. D. C. Caldwell: Radioactive Isotopes in a Chemical Laboratory. (Erasmus Wilson demonstration.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Pathology*. Dr. D. A. Mitchison, Dr. R. J. W. Rees, Dr. John Marks: Acid-fast Bacilli.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. R. G. Bannister: Anhidrosis and Heat Illness.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Dr. H. Gardiner-Hill: Obesity in Women.

Wednesday, 18th

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *General Practice*. Dr. J. A. Currie, Mr. C. Gill-Carey, Dr. Denis Williams: Vertigo.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. L. G. Lajtha: Culture of Bone-marrow.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. J. O. Oliver: Modern Methods of Sterilisation.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. N. Lloyd Rusby: Sarcoidosis.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Prof. John McMichael: Lungs in Heart-disease.
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.30 P.M. Mr. T. E. Cawthorne: Medicine in Art. (Presidential address.)

Thursday, 19th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Dr. Pond: Psychiatric Aspects of Epileptic Brain Damaged Children. (Second of two Goulstonian lectures.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. P. N. Magee: Biochemical and Pathological Mechanisms in Experimental Liver Cancer.
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. P. B. Kunkler, Dr. P. E. Thompson Hancock, Dr. J. D. N. Nabarro: Treatment of the Reticuloses by Chemotherapy and Radiotherapy.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Dr. Thomas Wilson: Filariasis in Malaya.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Prof. Alex Haddow: Present Situation in Cancer Research.
NUFFIELD ORTHOPÆDIC CENTRE, WINGFIELD-MORRIS ORTHOPÆDIC HOSPITAL, Oxford
8.30 P.M. Mr. W. J. W. Sharrard: Place of Orthopædic Surgery in Cerebral Palsy.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Prof. G. A. Smart: Auto-immune Thyroiditis.

Friday, 20th

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine*. Dr. J. S. Lawrence: Epidemiological Studies on Rheumatoid Arthritis in Northern Europe.
8.15 P.M. *Radiology*. Prof. Norman Ashton, Mr. H. B. Stallard, Dr. Manuel Lederman: Pigmented Tumours of the Eye.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. Wylie McKissock: Aspects of the Surgery of Intracranial Hæmorrhage.
4 P.M. Dr. M. D. Milne: Renal Tubular Transport Defects.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. Wallace Black: Vasomotor and Allergic Rhinitis.
FACULTY OF RADIOLOGISTS
4.30 P.M. (Royal College of Surgeons of England.) *Radiology*. Prof. D. W. Smithers, Dr. D. H. Nelson, Dr. Martin Bodian, Dr. H. J. Whiteley: Spontaneous Regression of Tumours.
PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (North Friary House.) Prof. J. Chassar Moir: English Queens and their Confinements.